Module 2.5

Clinical Overview

TABLE OF CONTENTS

PAGE

ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir Sulfate
ACCEPT	General Treatment Acceptance Score
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BCRP	Breast cancer resistance protein
BMI	Body Mass Index
CAB	Cabotegravir
CAR	Continued/Current Antiretroviral Regimen
CD	Cluster of Differentiation Cells
CI	Confidence Interval
CK	Creatine Kinase
CL/F	Oral Clearance
Cmax	Maximum observed plasma drug concentration
c/mL	Copies per milliliter
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
$C\tau$	Trough plasma concentrations at the end of the dosing
CVF	Confirmed Virologic Failure
DDI	Drug-drug Interaction
DILI	Drug-induced Liver Injury
DTG	Dolutegravir
DTG/ RPV FDC	Dolutegravir and Rilpivirine Fixed-dose Combination
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
EU	European Union
FDC	Fixed-dose Combination
FTC	Emtricitabine
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1

HIVTSQc	HIV Treatment Satisfaction Questionnaire Change Version
HSR	Hypersensitivity Reaction
IFU	Instructions for Use
IM	Intramuscular
INI	Integrase Inhibitor
INSTI	Integrase Strand Transfer Inhibitor
ISE	Integrated Summary of Efficacy
ISR	Local Injection Site Reaction
ISS	Integrated Summary of Safety
ITTE	Intent-to-treat Exposed
Janssen	Janssen Sciences Ireland UC
L	Liter
LA	Long-acting Injectable, Extended Release Suspension for Injection, or Prolonged Release Suspension for Injection
LLQ	Lower limit of quantification
LOCF	Last Observation Carried Forward
LSC	Liver Stopping Criteria
LSLV	Last Subject Last Visit
LTFU	Long Term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
MRHD	Maximum Recommended Human Dose
ms	millisecond
MVA	Multivariable analysis
ng	Nanogram
nm	Nanometer
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAID	Nonsteroidal Anti-inflammatory Drugs
OLI	Oral Lead In
OR	Odds Ratio
PBMC	Peripheral blood mononuclear cell
Pgp	P-glycoprotein
PI	Protease Inhibitor
PIN	Perception of Injection
PK	Pharmacokinetics
PP	Per protocol
Q4W	Dosing once every 4 weeks
Q8W	Dosing once every 8 weeks
QTc	Corrected QT Interval
QTcB	Heart Rate-corrected QT Interval
QTcF	QT Interval Corrected using Fridericia's Formula
RAL	Raltegravir
RNA	Ribonucleic Acid

RPV	Rilpivirine (TMC278)
SAE	Serious Adverse Event
SC	Subcutaneous
SOC	Standard of Care
SVF	Suspected Virologic Failure
$T_{1/2}$	Terminal phase half-life
TDF	Tinofovir Disoproxil Fumarate
Tmax	Time of occurrence of Cmax
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
Vc/F	Apparent volume of the central compartment

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1. PRODUCT DEVELOPMENT RATIONALE

CAB is part of a new, 2-drug, monthly or every 2 months dosing regimen with RPV for the treatment of HIV-1 infection in adults. This submission focuses on the CAB component of this 2-drug regimen. RPV is owned by Janssen Sciences Ireland UC (Janssen) and is the subject of a separate marketing application.

1.1. Introduction

The overall objective of the CAB + RPV clinical program is to develop a novel, highly effective, well tolerated 2-drug LA injectable regimen. Such a regimen offers reduced dosing frequency (monthly or every 2 months) compared with daily oral ARVs. With less frequent dosing, the daily reminder of the patient's HIV status may be avoided, and associated stigma related to taking oral treatment regimens may be lessened. A reduced dosing schedule holds promise for increased patient compliance with dosing requirements. This novel treatment option may result in improved overall satisfaction with treatment and longer retention in care for individuals with HIV infection. This NRTI-sparing regimen avoids exposure to this class of ART thereby avoiding possible NRTI-class-related resistance, and longer term NRTI-related toxicities. Given the parenteral route of administration, a 2-drug LA injectable regimen may result in fewer gastrointestinal adverse events, eliminates dosing restrictions with regard to food, and will have fewer drug-drug interactions at the level of the gastrointestinal tract.

If approved, this will be the first 2-drug LA injectable regimen for maintaining viral suppression. Current therapies and unmet medical need are discussed further in Section 6.1.2

CAB is a potent INSTI that possesses attributes that allow formulation and delivery as an LA parenteral product for IM administration. An oral tablet formulation of CAB has also been developed and will be used in combination with oral RPV as part of a 1-month OLI before LA therapy is initiated or as oral bridging. CAB has a high barrier to the selection of INSTI-resistant mutations. While CAB resistance has been infrequently observed in clinical trials, the resultant viruses have typically shown full susceptibility to DTG.

1.2. Summary of Clinical Development Program

ViiV Healthcare in partnership with Janssen Sciences Ireland UC (Janssen) are developing the CAB + RPV regimen for the treatment of HIV-1 infection. ViiV Healthcare is the Sponsor of the CAB + RPV clinical program. Various aspects of the program are being conducted by GSK on behalf of ViiV Healthcare.

The summaries of efficacy and safety are based on the pooled primary analyses of the ongoing Phase III studies at Week 48 (Study 201584 and Study 201585) comparing monthly (Q4W) dosing with oral SOC and analyses of the Phase IIIb study at Week 48 (Study 207966) comparing every 2 months (Q8W) dosing with monthly dosing. The Phase III/IIIb randomized studies represent the proposed regimen and dosages intended for commercial use and enable an assessment of benefit-risk based on the comparative

efficacy and safety data from these 3 studies. Supportive efficacy information from the Week 96 timepoint in Study 201584 and supportive safety information from the Week 96 timepoint in the Phase III studies (201584 and 201585) and from the Phase II studies (LAI116482 [oral] and 200056 [LA]) are presented in this application.

Overall, 2382 subjects have been exposed to oral CAB or CAB LA in the CAB Phase I program and CAB + RPV Phase II and Phase III studies in HIV-infected subjects (Table 1). In total, 509 subjects from 19 integrated CAB clinical pharmacology studies were pooled in a separate safety analysis (m2.7.4 Section 5.5.1). Across the 2 Phase II studies, 181 subjects (Study 116482: GSK Document Number 2014N216014_00) and 309 subjects (Study 200056: GSK Document Number 2018N380094_00) were enrolled and received either CAB or CAB + RPV. Across the 2 Phase III studies (Study 201584: GSK Document Number 2017N345267_00 and Study 201585: GSK Document Number 2018N370336_00), 591 subjects were randomized to receive CAB + RPV. In the Phase IIIb Study 207966 (GSK Document Number 2019N406358_01), 792 additional subjects received CAB + RPV (excluding those subjects who transitioned from Study 201585).

Table 1 Summary of Key Clinical Studies

Study	Study Design	Population	Treatment details
201584 (FLAIR) Status: Ongoing; Week 96 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC	HIV-1 infected ART-naïve adult subjects	**Induction Phase (20 weeks):** Oral ABC/DTG/3TC FDC (NRTI substitution allowed) **Maintenance Phase (100 weeks):** CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs) **Extension Phase and beyond:** Details are provided in the CSR.
201585 (ATLAS) Status: Ongoing; Week 96 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen	HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (52 Weeks):** CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) Control group: 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI. **Extension Phase and beyond:** Details are provided in the CSR.
207966 (ATLAS-2M) Status: Ongoing; Week 48 CSR completed	Open-label, randomized, Phase IIIb trial to demonstrate non-inferiority of LA CAB + LA RPV Q8W compared with LA CAB + LA RPV Q4W	HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (52 Weeks):** CAB + RPV Q4W group: CAB LA 600 mg + RPV LA 900 mg initiation dose*, CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) CAB + RPV Q8W group: CAB LA 600 mg + RPV LA 900 mg initiation dose*, CAB LA 600 mg + RPV LA 900 mg second initiation dose* administered 4 weeks after the initial dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks (±7 days) *Note: Subjects were either transitioned from Study 201585 (CAB + RPV Q4W or SOC) or from their current SOC. Those transitioning from SOC received oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks followed by appropriate initiation doses. Those transitioning from CAB + RPV Q4W received OLI and initiation doses during their participation in Study 201585 and started

Study	Study Design	Population	Treatment details
			maintenance doses on Day 1 of Study 207966 according to their randomization assignment. **Extension Phase and beyond:** Details are provided in the CSR
200056 (LATTE-2) Status: Ongoing; Week 96 CSR completed, Week 160 CSR completed	Open-label, randomized, dose ranging, Phase IIb trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression	HIV-1 infected ART-naïve adult subjects	**Induction Phase (20 weeks):** Oral CAB 30 mg + ABC/3TC once daily. With oral RPV 25 mg once daily for last 4 weeks **Maintenance Phase (96 weeks):** CAB + RPV Q4W group: CAB LA 800 mg + RPV LA 600 mg initiation dose, CAB LA 400 mg + RPV LA 600 mg every 4 weeks CAB + RPV Q8W group: CAB LA 800 mg + RPV LA 900 mg initiation dose, CAB LA 600 mg second dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks Control group: Oral CAB 30 mg + ABC/3TC once daily **Extension Phase and beyond**: Details are provided in the CSR.
LAI116482 (LATTE) Status: Completed; Week 96 CSR completed; Week 144 SCSR completed; Final (EOS) CSR Completed	Randomized, partially blind dose ranging, Phase IIb trial evaluating oral CAB in combination with oral RPV	HIV-1 infected ART-naïve adult subjects	**Induction Phase (24 weeks):** CAB group: Oral CAB 10, 30, or 60 mg + ABC/3TC or TDF/FTC once daily Control group: EFV + ABC/3TC or TDF/FTC **Maintenance Phase (72 weeks):** CAB + RPV group: Oral CAB 10, 30, or 60 mg + oral RPV 25 mg once daily Control group: EFV + ABC/3TC or TDF/FTC **Open-Label Phase (post 96 weeks)**: CAB 30 mg + RPV 25 mg

1.3. Regulatory History

The CAB + RPV development program has been formally discussed with regulatory agencies at various milestones throughout development (see m1 and m2.2).

1.4. Claimed Indication and Dosage

1.4.1. Oral Tablets

CAB tablets are indicated in combination with RPV tablets for short term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL) and have no known or suspected resistance to either CAB or RPV for use as:

- OLI to assess tolerability of CAB prior to administration of LA CAB injection.
- Oral therapy (bridging) for patients who will miss planned dosing with CAB injection.

The proposed recommended oral dose for CAB is 30 mg (1 tablet) administered with oral RPV 25 mg (1 tablet) once daily with a meal.

1.4.1.1. OLI

CAB oral tablets are recommended for approximately one month (at least 28 days) in virologically suppressed patients prior to the initiation of CAB injection to assess tolerability to CAB. CAB tablets should be taken with RPV tablets.

1.4.1.2. Oral Therapy (Bridging)

If a patient plans to miss a scheduled monthly injection visit by more than 7 days, CAB tablets (30 mg) may be used in combination with RPV tablets (25 mg) once daily to replace up to 2 monthly injection visits. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CAB or RPV. Injection dosing should be resumed on the day oral dosing completes.

If a patient plans to miss a scheduled every-2-months injection visit by more than 7 days, CAB tablets (30 mg) may be used in combination with RPV tablets (25 mg) once daily to replace 1 every-2-months visit. The first dose of oral therapy should be taken approximately two months after the last injection dose of CAB and RPV. Injection dosing should be resumed on the day oral dosing completes.

1.4.2. Injection

CAB injection is indicated in combination with RPV injection for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL) without prior treatment failure and have no known or suspected resistance to either CAB or RPV (Table 3).

When administering the CAB injections, healthcare providers should take into consideration the BMI of the patient to ensure that the needle length is sufficient to reach the gluteus muscle.

Table 2 Proposed CAB Commercial LA Monthly Dosing Regimen, When Used with RPV

Dosing Schedule	Drug	OLI	Initiation Injection	Continuation Injection
		For 1 Month (at Least 28 Days)	At Month 2	At Month 3 and Onward
Monthly	CAB	30 mg once daily with a meal	3 mL (600 mg)	2 mL (400 mg) monthly
	RPV	25 mg once daily with a meal	3 mL (900 mg)	2 mL (600 mg) monthly

Note: In Study 201584 and Study 201585 protocols, the 3 mL injections were referred to as "First Injections (Loading Dose)" and the 2 mL injections were referred to as "Maintenance Injections."

Table 3 Proposed CAB Commercial LA Every 2 Months Dosing Regimen, When Used with RPV

Dosing Schedule	Drug	OLI	Initiation Injections (1 Month Apart)	Continuation Injections (2 Months Apart)
		For 1 Month (at Least 28 Days)	At Month 2 and Month 3	At Month 5 and Onward
Every 2 months	CAB	30 mg once daily with a meal	3 mL (600 mg)	3 mL (600 mg) every 2 months
	RPV	25 mg once daily with a meal	3 mL (900 mg)	3 mL (900 mg) every 2 months

1.5. Compliance with GCP

All studies were undertaken in accordance with standard operating procedures of ViiV Healthcare and the GlaxoSmithKline Group of Companies, which comply with the principles of GCP. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

2. OVERVIEW OF BIOPHARMACEUTICS

The proposed commercial formulations of CAB 30 mg tablets and CAB LA were used in the Phase III studies.

The sterile, neutral [redacted] CAB LA formulation provides prolonged release of the active moiety after IM injection.

For detailed information on biopharmaceutic data described in this section, refer to m2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods).

2.1. Formulation Development

For detailed information on CAB formulation development, refer to m3 (Quality).

2.1.1. CAB LA

During the development of the IM CAB LA formulation, an isotonic, aqueous injectable suspension was selected and used in Phase I, Phase II, and Phase III clinical trials.

CAB LA is formulated as an injectable suspension containing 200 mg/mL of CAB free acid with median particle size of [redacted] nm. CAB LA is provided as a sterile white to light pink, free-flowing suspension, packaged in a single use USP Type I glass vial with a 13-mm grey stopper and aluminum seal. Each vial contains a nominal fill of 2.0 mL or 3.0 mL and does not require dilution prior to administration. Each sterile, single-use vial of CAB LA 200 mg/mL is intended to provide a dose of 400 mg/2 mL or 600 mg/3 mL for IM administration.

2.1.2. Oral CAB

During development of the oral formulation, different tablet formulations were investigated, and the formulation chosen for Phase III clinical trials and the commercial product is a white, film-coated, tablet containing [redacted] CAB as the sodium salt, equivalent to 30 mg of CAB as the free acid.

CAB can be taken with or without food. When dosed together, oral CAB + oral RPV should be taken with a meal.

2.2. In Vitro Dissolution Data

For detailed information on in vitro dissolution, refer to m2.7.1 and m3.

2.3. Analytical Methods

The bioanalytical methods used to measure concentrations of CAB in human plasma, in the presence of RPV, were sensitive, accurate and reproducible (m2.7.1 Section 1.5).

2.4. Biopharmaceutics Studies

The key results of the biopharmaceutic studies for CAB LA are detailed in m2.7.1 Section 2.

The long-term stability studies conducted with CAB LA have confirmed that it can be stored at or below 30°C (86°F) with a precautionary statement of do not freeze (m3.2.P.8 Stability).

The results of study LAI116815 showed that the [redacted] of the CAB LA formulation provided the desired PK profile (i.e., the release rate) after IM injection (m2.7.1 Section 2.2.2). However, in vitro, an inverse relationship was observed between [redacted] and [redacted], i.e., as [redacted].

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Critical findings from the clinical pharmacology studies conducted with CAB are discussed in this section. These studies are described in detail in m2.7.2 (Summary of Clinical Pharmacology).

3.1. Key Characteristics of Clinical Pharmacology for CAB

Table 4 Key Pharmacokinetic Characteristics of CAB

	CAB	
	Oral	**LA**
Absorption		
Relative bioavailability of oral to LA	0.756	
Tmax	3 hours	7 days
Effect of moderate-fat meal (relative to fasting): AUC(0-inf) Ratio	1.08 (0.978, 1.20)	NA
Effect of high-fat meal (relative to fasting): AUC(0-inf) Ratio	1.14 (1.02, 1.28) Administer oral CAB with or without food	NA
Polyvalent cations	Chelation effect in vitro ↓plasma CAB exposure; dose separation with antacids	NA
Distribution		
% bound to human plasma proteins	>99.8	
Blood-to-plasma ratio	0.52	
Cervical tissue-to-plasma ratio	0.16 - 0.20	
Vaginal tissue-to-plasma ratio	0.19 - 0.28	
Rectal tissue-to-plasma ratio	0.00 - 0.08	
CSF-to-plasma ratio	0.003 (CSF-to-plasma unbound >1.0)	

	CAB	
	Oral	**LA**
Metabolism		
Metabolism	UGT1A1 UGT1A9 (minor)	
Elimination		
Major route of elimination	Metabolism	
CL/F	0.21 L/h	0.151 L/h
t1/2	41 hours	5.6 to 11.5 weeks
% of dose excreted as total radioactivity (unchanged drug) in feces	58.5 (46.8)	ND
% of dose excreted as total radioactivity (unchanged drug) in urine	26.8 (0)	ND

Data Source: m2.7.2 In-Text Table 1.
Note: Additional information and Table Footnotes are provided in m2.7.2 In-text Table 1.

3.1.1. Absorption

Following single dose administration of CAB LA 800 mg IM, plasma CAB concentrations were quantifiable by the first PK sampling time point (4 hours post injection) and gradually rose to reach Cmax at approximately 7 days (m2.7.2 Section 3.2.6.1). High variability in plasma CAB tmax (range of 2 to 213 days across all dose levels) was evident in Study LAI114433, a study that incorporated long-term PK sampling following administration of single doses of CAB LA.

CAB LA exhibits absorption rate-limited (flip-flop) PK because CAB is slowly absorbed into the systemic circulation following IM injection into the gluteus medius muscle and the rate of absorption following IM administration of CAB LA (0.000733 h^{-1}) is much slower than the rate of CAB elimination from plasma (m2.7.2 Section 3.2.6.1). CAB LA absorption rate-limited PK is reflected in a long apparent t1/2. The PopPK estimate of plasma CAB half-life after IM dosing was 5.6 weeks for males and 11.5 weeks for females, compared with a t1/2 of 41 hours, representing systemic elimination, following oral CAB.

CAB is rapidly absorbed following oral administration, with an absorption rate of 1.41 h^{-1} and a median tmax of 3 hours (m2.7.2 Section 3.2.6.1). The absolute bioavailability of oral CAB is predicted to be high based on low CL/F (0.151 L/h), a relative bioavailability of 76% compared with CAB LA, and minimal impact of food on plasma CAB absorption (exposure) and absorption rate. Because food had minimal impact on plasma CAB exposure following oral dosing, CAB may be taken with or without food.

HIV INIs are known to chelate with polyvalent cations, resulting in decreased absorption; chelation was demonstrated for CAB in vitro (m2.7.2 Section 3.2.6.1). In CAB Phase III studies, antacids containing divalent cations were to be administered at least 2 hours

before or 4 hours after oral CAB doses if needed. Dose separation is not relevant for CAB LA, which is administered IM, because the interaction with oral CAB occurs in the GI tract.

3.1.2. Distribution

In humans, the estimate of plasma CAB Vc/F was 5.27 L and Vp/F was 2.43 L (m2.7.2 Section 3.2.6.2). These volume estimates, along with the assumption of high F, suggest some distribution of CAB to the extracellular space.

Following single dose administration of CAB LA 400 mg IM, the median cervical tissue:plasma ratio was 0.16 to 0.20 and the vaginal tissue:plasma ratio 0.19 to 0.28 (m2.7.2 Section 3.2.6.2). Median CAB concentrations in cervical and vaginal tissues were approximately equivalent to the in vitro PA-IC90 (0.166 µg/mL) at 4, 8, and 12 weeks after dosing, assuming a density of 1 g of tissue/mL of homogenate. CAB concentrations in rectal tissue were lower than in cervical and vaginal tissues.

One week following a steady-state CAB LA (Q4W or Q8W) injection, median concentrations of CAB in the CSF were higher than corresponding median unbound CAB concentrations in plasma, suggesting that therapeutic CAB concentrations are achieved in the CSF (m2.7.2 Section 2.1.2.5). Consistent with therapeutic CAB concentrations in the CSF, CSF HIV-1 RNA concentrations were <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA concentrations were <50 c/mL in 100% and <2 c/mL in 12/18 (66.6%) of subjects.

CAB is highly bound to human plasma proteins based on ex vivo and in vitro data. In healthy subjects with normal organ function, the median CAB unbound fraction was 0.11 to 0.166% (99.8 to 99.9% bound) (m2.7.2 Section 3.2.6.2). In HIV-1-infected subjects, the median CAB unbound fraction was 0.075 to 0.103% (99.9% bound). The ex vivo unbound fraction estimate is lower than the in vitro estimate of 0.62% (99.4% bound). In vitro protein binding was independent of CAB concentrations over the range of 1 to 20 µg/mL, but a lower unbound fraction of 0.47% (99.5% bound) was observed at 0.50 µg/mL (m2.6.4 Section 4.1.1). Ex vivo plasma unbound fraction was higher in subjects with hepatic impairment and renal impairment.

Blood total radiocarbon was approximately 52% of plasma radiocarbon AUC(0-inf) (m2.7.2 Section 3.2.6.2). The low radiocarbon concentrations in blood suggest minimal association of CAB with red blood cells.

CAB is a substrate of Pgp and BCRP, but because of its high permeability no alteration in oral absorption would be expected by co-administration of either Pgp or BCRP inhibitors (m2.6.4 Section 9).

3.1.3. Metabolism

The metabolism of CAB was characterized by in vitro, ex vivo, and in vivo studies with oral formulations. The pathway(s) and extent of CAB metabolism are independent of formulation and route of administration (m2.7.2 Section 3.2.6.3).

In the human mass balance study, CAB was the predominant circulating metabolite in plasma, representing 80.5 to 100% of plasma total radiocarbon in pooled plasma samples collected 2 to 24 hours post-dose and the majority of the plasma radiocarbon AUC(0-inf); no metabolites were quantified in pooled plasma samples (m2.7.2 Section 3.2.6.3). Based on metabolic profiling in urine, feces, and bile, glucuronidation leading to formation of GSK3388352 (M1) is the primary metabolic pathway, accounting for 20% of the administered dose. Glucose conjugation leading to formation of M2 is a minor pathway for CAB metabolism; M2 was detected, but not quantified, in urine. Unchanged CAB and GSK3388352 (M1) were detected in duodenal bile samples.

CAB is the major component in plasma and the glucuronic acid metabolite is the predominant component in urine, regardless of route of administration (m2.7.2 Section 3.2.6.3 In-text Table 111).

Oxidation of CAB accounts for <1% dose in humans (m2.7.2 Section 3.2.6.3). In human studies LAI115428 and LAI114433, mass spectrometric analyses determined that M3 (a metabolite formed by oxidation, fluorine loss and cysteine conjugation) represented <1% of the drug-related material present in the urine following oral, IM, and SC administration.

3.1.4. Excretion

Following single dose administration of [^{14}C]-CAB 30 mg oral solution in humans, 85.3% of the administered dose was recovered in the excreta; 58.5% of the dose was recovered in feces and 26.8% was recovered in urine (m2.7.2 Section 3.2.6.4). CAB accounted for 46.8% of the administered dose in feces and was not detected in urine. The glucuronide metabolite GSK3388352 (M1) represented the majority of the radioactivity recovered in urine. Both CAB and GSK3388352 were detected in bile.

CAB is a low clearance drug; from the PopPK analysis, the estimate of plasma CAB CL/F was 0.151 L/h (m2.7.2 Section 3.2.6.4). Oral CAB has a terminal half-life of approximately 41 hours, which is consistent with low clearance. CAB LA has a longer apparent t1/2 due to absorption rate-limited PK.

From the PopPK analysis, following discontinuation of the CAB LA Q4W regimen (administered to steady-state), 47% of patients overall were predicted to have quantifiable plasma CAB concentrations (>LLQ [0.025 µg/mL]) 1 year after the last IM injection and 17% of patients overall were predicted to have quantifiable plasma CAB concentrations 96 weeks after the last IM injection (m2.7.2 Section 3.2.6.4). In the Phase IIb Study 200056, 4 of 12 subjects presenting for the 12-month follow-up visit had quantifiable CAB concentrations ranging from 0.045 to 0.083 µg/mL (all below the in vitro PA-IC90 of 0.166 µg/mL), and CAB was below the LLQ of 0.025 µg/mL for the remaining 8 subjects.

3.2. Pharmacokinetics in Healthy Subjects and Target Patient Populations

Based on accumulated data, there appears to be no significant difference in the PK of CAB between healthy and HIV-infected subjects (m2.7.2 Section 3.2.1).

3.2.1. Summary of PK Parameters for CAB

The proposed monthly and every 2 months CAB regimens achieve plasma concentrations similar to those from efficacious oral CAB 10 mg and 30 mg once daily doses (Table 5).

Table 5 Summary (Geometric Mean [5th, 95th Percentile]) of CAB PK Parameters Following Administration of Proposed CAB + RPV Regimen in HIV-infected Subjects

Drug	Dosing Phase [a]	Dosage Regimen	Plasma CAB PK Parameter		
			AUC(0-tau) (μg•h/mL)	Cmax (μg/mL)	Ctau (μg/mL)
CAB	Oral Lead-In[a]	30 mg PO once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
	Initial Injection[b]	600 mg IM initial dose	1,591 (714, 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
	Monthly Injection[c]	400 mg IM monthly	2,415 (1,494, 3,645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
	Every 2 Months Injection[c]	600 mg IM every 2 months	3764 (2431, 5857)	4.02 (2.26, 6.83)	1.61 (0.80, 2.99)

Data Source: m2.7.2 In-text Table 118.

a. OLI PK parameter values represent steady-state.
b. Initial Injection Cmax values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose.
c. Monthly and every 2 months injection PK parameter values represent Week 48 (11th injection for monthly and 6th injection for every 2 months).

PK parameter values were based on individual post-hoc estimates from the final PopPK model and are presented as geometric mean (5th, 95th percentile).

Similar plasma CAB exposure between healthy and HIV-1-infected subjects supports extrapolation of data generated in healthy subjects, such as drug and food interactions and the TQT study, to the HIV-1-infected population. Plasma CAB PK parameter values following administration of CAB LA and oral CAB are similar between healthy and HIV-1-infected subjects based on results of cross-study comparisons (m2.7.2 Section 3.2). Consistent with this, population (healthy compared with HIV) was not a significant covariate in the PopPK analysis.

Overall, plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat dose administration of CAB LA 100 to 800 mg IM and oral CAB 5 to 60 mg (m2.7.2 Section 3.2.2). Following single dose administration of

a higher dose of oral CAB 150 mg, geometric mean plasma CAB Cmax (10.4 μg/mL) and AUC(0-inf) (418 μg.h/mL) were markedly lower than expected compared with oral CAB 30 mg (geometric mean Cmax of 3.61 μg/mL and AUC(0-inf) of 146 μg.h/mL).

For CAB LA, time to steady-state is driven by administration of a higher initial dose and the absorption rate following IM injection (m2.7.2 Section 3.2.3). The time to steady-state was approximately 44 weeks following administration CAB LA as an initial dose (800 mg or 600 mg IM) on Day 1 followed by 400 mg IM Q4W in Phase III Studies 201585 and 201584. The time to achieve steady-state is prolonged with CAB LA with efficacious concentrations achieved following the initial dose.

Steady-state plasma CAB concentrations are achieved by Day 7 following once daily administration of oral CAB in HIV-1-infected subjects (m2.7.2 Section 3.2.3), consistent with the approximate 2.5-fold accumulation and a t1/2 of approximately 41 hours.

Based on cross-study comparison, plasma CAB PK is time-invariant because plasma CAB AUC(0-tau) following repeat dosing was similar to AUC(0-inf) following single dose administration of oral CAB (m2.7.2 Section 3.2.4).

Moderate between-subject variability (%CVb) in plasma CAB PK was observed following repeat-dose administration of CAB (m2.7.2 Section 3.2.5.1). Following administration of CAB LA 400 mg Q4W in healthy or HIV-1 infected subjects, between-subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 26 to 39% across studies. Following administration of oral CAB 30 mg once daily, between-subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 26 to 34% across healthy subject studies and 28 to 56% across HIV-1 infected subject studies. Higher between-subject variability (41 to 89%) in plasma CAB PK was observed with single dose administration of CAB LA.

Within-subject variability (%CVw) in plasma CAB PK was low following administration of oral CAB (m2.7.2 Section 3.2.5.2). Within-subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 7 to 11% following repeat dose administration of oral CAB 30 mg once daily. Plasma CAB AUC(0-inf), Cmax, and C24 ranged from 13 to 32% following single-dose administration of oral CAB 30 mg. Within-subject variability data are not available for CAB LA because CAB LA studies were parallel design.

3.3. PK in Special Populations

Clinical studies to evaluate CAB PK in special populations were conducted using oral formulations (m2.7.2 Section 2.6.5). CAB PK following oral administration in special populations can be extrapolated to the LA formulations. Select clinically relevant intrinsic and extrinsic factors were evaluated in population PK models to identify covariates affecting CAB PK.

The impact of covariates on the PK of CAB after IM dosing was evaluated in the population PK analysis based on the studies with the LA products (m2.7.2 Section 2.2).

3.3.1. Hepatic Impairment

No dosage adjustment of CAB is required for patients with mild or moderate hepatic impairment (m2.7.2 Section 2.6.5.1). Moderate hepatic impairment had minimal impact on plasma CAB Cmax and AUC(0-inf) and geometric mean (90% CI) plasma CAB C2h_unb in subjects with moderate hepatic impairment was 1.40-fold (0.798, 2.46-fold) the value in healthy subjects. This increase in plasma CAB C2h_unb (approximate Cmax_unb) is not considered clinically relevant based on safety observed with higher doses. Given that plasma CAB Cmax is lower following LA administration, subjects with mild or moderate hepatic impairment would be expected to have lower unbound Cmax than observed following oral dosing. CAB has not been studied in patients with severe hepatic impairment. Limited data is available in patients with hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

3.3.2. Renal Impairment

CAB may be administered without dose adjustment in patients with mild, moderate, or severe renal impairment (CLcr <30 mL/min, not on dialysis) (m2.7.2 Section 2.6.5.2). Severe renal impairment had minimal impact on plasma CAB Cmax and AUC(0-inf) and geometric mean (90% CI) plasma CAB C2h_unb in subjects with severe renal impairment was 1.32-fold (0.807, 2.15-fold) the value in healthy subjects. This increase in plasma CAB C2h_unb (approximate Cmax_unb) is not considered clinically relevant based on safety observed with higher doses.

CAB has not been studied in subjects with end-stage renal disease on renal replacement therapy (m2.7.2 Section 3.2.8.2). CAB is not expected to be cleared by renal replacement therapies, such as hemodialysis or peritoneal dialysis, due to CAB's high protein binding (>99%) and because absorption is slow from the CAB LA IM depot site, such that minimal drug would be available to dialysis.

3.3.3. UGT1A1 Polymorphisms

Genetically predicted UGT1A1 activity was associated with plasma CAB PK parameters following CAB LA and oral CAB, supporting that glucuronidation in the liver is an important metabolic pathway for both CAB LA and oral CAB (m2.7.2 Section 3.2.8.3). The magnitude of difference among the UGT1A1 activity categories was not clinically relevant. The UGT1A9 genetic variant (*1B) was not associated with plasma CAB PK.

3.3.4. Population PK

There were no covariates with clinically relevant impact on the PK of CAB after IM dosing (e.g., gender, race, age [≥18 years of age], metabolic enzyme polymorphisms, BMI) (m2.7.2 Section 2.2). The PK of CAB has not been studied in adolescents and children (<18 years of age).

CAB may be administered without dose adjustment in adults regardless of age, gender, race, body size (weight, BMI), or metabolic enzyme polymorphism (m2.7.2 Section 3.2.8.3).

Of the 1647 subjects included in the CAB PopPK analysis, 424 (25.7%) were female, the median (min-max) age was 36 years (18-74 years), 20 subjects (1.2%) were ≥65 years of age, 1102 (66.9%) were White, 394 (23.9%) were Black/African American, 56 (3.4%) were Asian, and 5.7% were of other (or unknown) races (m2.7.2 Section 3.2.8.3). A total of 11,443 (94%) of 12,169 CAB injections were administered unsplit. Needle length ranged from 1 to 2.5 inches, but the 1.5-inch needle length was predominantly used (representing 88.5% of all available needle length data), regardless of BMI.

CAB PK variability was explained by gender, BMI, needle length, and split injection, which were statistically significant covariates of CAB LA absorption rate (KA2), and current smoker status, which was a statistically significant covariate of CAB CL/F (weight scaling on CL/F, V2/F, Q/F, and V3/F was also implemented) in the final CAB PopPK model; however, the effects of these covariates are not considered clinically relevant (m2.7.2 Section 3.2.8.3).

Age and race had no effect on CAB PK and no dose adjustment is needed; CAB PK data in subjects of >65 years old and some racial groups are limited (m2.7.2 Section 3.2.8.3).

Phase IIb and Phase III protocols recommended a 1.5-inch needle length for most subjects and stated that longer needle lengths may be required for participants with higher BMIs (example >30 kg/m^2) to ensure that injections were administered IM as opposed to subcutaneously (m2.7.2 Section 3.2.8.3). Use of a longer needle in high BMI subjects had minimal impact on plasma CAB exposure parameters based on PopPK analysis, but these results may not be robust given the limited number of subjects with high BMI using needles longer than 1.5 inches in Phase III studies.

3.4. Drug-Drug Interactions

Given the pathways of metabolism and elimination of CAB are independent of formulation and route of administration, and because plasma CAB concentrations achieved with the CAB LA Q8W or Q4W regimen are within the range of concentrations achieved with oral CAB 10 mg to 30 mg once daily, results from oral DDI studies can be used to inform the recommendations for CAB LA, when used with RPV LA (m2.7.2 Section 2.6.6).

CAB (LA and Oral):

- CAB is contraindicated with the UGT1A1 inducers RIF, rifapentine, CBZ, oxcarbazepine, phenobarbital, and phenytoin due to potential for loss of therapeutic effect and development of resistance. CAB LA is contraindicated with RBT because RBT may decrease CAB plasma concentrations.
- There is not a significant drug interaction between CAB and RPV, the 2 components of the regimen.

- Because of the low DDI liability for CAB as perpetrators, there are no co-medications that require dose adjustment when given together with CAB and there are no DDI limitations to the ARV regimens that can be given after discontinuation of CAB.
- No dose adjustments are needed for CAB when co-administered with UGT or CYP inhibitors.

CAB (Oral Only):

- Antacids containing polyvalent cations must be administered at least 2 hours before or 4 hours after oral CAB.

3.4.1. Effect of Other Agents on the PK of CAB and Dose Recommendations

Results from oral CAB drug interaction studies can be extrapolated to CAB LA because pathways of CAB metabolism and elimination and the extent of CAB metabolism are independent of formulation and route of administration and because plasma CAB concentrations achieved with the CAB LA Q4W regimen are within the range of concentrations achieved with oral CAB 10 mg to 30 mg once daily (m2.7.2 Section 3.2.9).

Except for strong inducers of UGT1A1, such as RIF, and chelation with antacids containing divalent cations (applicable to oral CAB only), CAB is not expected to be a victim of clinically meaningful drug interactions (Table 6).

Table 6 Effects of Concomitant Medications on CAB Pharmacokinetics

Concomitant Drug Regimen	N	Oral CAB Regimen	Geometric Mean Ratio (90% CI) of CAB PK parameters with/without co-administered drugs No Effect = 1.00			Study	Clinical Recommendation
			Ctau	AUC	Cmax		
RIF 600 mg Once Daily	15	30 mg Single Dose	ND	0.41 (0.36, 0.46)	0.94 (0.87, 1.02)	LAI117010	Contraindicated Co-administration results in significant decreases in plasma CAB concentrations, which may result in loss of virologic response and possible resistance.
RBT 300 mg Once Daily	12	30 mg Once Daily	0.738 (0.702, 0.776)	0.786 (0.743, 0.831)	0.825 (0.761, 0.895)	205712	No dose adjustment[a]
ETR 200 mg BID	12	30 mg Once Daily	1.00 (0.94, 1.06)	1.01 (0.96, 1.06)	1.04 (0.99, 1.09)	ITZ111839	No dose adjustment[b]
RPV 25 mg Once Daily	11	30 mg Once Daily	1.14 (1.04, 1.24)	1.12 (1.05, 1.19)	1.05 (0.96, 1.15)	LAI116181	No dose adjustment

Data Source: m2.7.2 In-Text Table 113.
AUC=AUC(0-inf) for single dose CAB and AUC(0-tau) for repeat dose CAB.
a. CAB + RPV is proposed as a complete regimen; co-administration of rifabutin is contraindicated with RPV.
b. CAB + RPV is proposed as a complete regimen; co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. There are no DDI limitations to the ARV regimens that can be given after discontinuation of CAB + RPV.

3.4.1.1. CAB Dose Recommendations with UGT Inducers

In vitro and in vivo data indicate that CAB is primarily metabolized by UGT1A1 with some involvement from UGT1A9 (m2.7.2 Section 3.2.8.1). Oxidation of CAB accounts for <1% dose and therefore CAB is not subject to CYP-mediated interactions.

At the proposed doses, CAB must not be co-administered with strong inducers, such as rifampin, because plasma CAB concentrations are reduced to a clinically significant extent, which may result in loss of virologic response and possible resistance (Table 6). Based on results of the rifampin drug interaction study and the proposed CAB doses, CAB should not be co-administered with other strong inducers such as rifapentine, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin.

Co-administration of weak and moderate inducers, such as rifabutin and etravirine, do not reduce plasma CAB concentrations to a clinically relevant extent (Table 6). However, concomitant use of CAB LA + RPV LA with rifabutin is contraindicated because clinically relevant decreases in RPV are observed with rifabutin co-administration (m2.7.2 Section 3.2.9.1).

3.4.1.2. CAB Dose Recommendations with UGT Inhibitors

Results from the PGx analysis estimated a 40% higher plasma CAB AUC(0-tau) (~30% lower CL/F) in subjects with genetically predicted low UGT1A1 activity (m2.7.2 Section 3.2.8.4). PopPK simulations that implemented a 30% reduced plasma CAB CL/F inform the impact of reduced UGT activity on plasma CAB PK. Based on these data, plasma CAB Cmax is not predicted to exceed the Cmax observed with oral CAB 60 mg once daily. The impact of a UGT1A1 or UGT1A9 inhibitor has not been studied clinically, but no significant impact is expected based on the PGx and PopPK results as well as PBPK modeling of the impact of UGT inhibitors, where predicted increases in geometric mean plasma CAB AUC(0-tau) and Cmax were ≤11% when oral CAB 30 mg once daily was co-administered with ATV (UGT1A1 inhibitor) or mefenamic acid (UGT1A9 inhibitor).

3.4.1.3. CAB Dose Recommendations with Antacids Containing Polyvalent Cations

HIV INIs are known to chelate with polyvalent cations, resulting in decreased absorption. Chelation was demonstrated for CAB in vitro with results similar to DTG (m2.7.2 Section 3.2.9.1).

In Phase III studies, antacids containing polyvalent cations were to be administered at least 2 hours before or 4 hours after oral CAB doses (for consistency with the recommendation for oral RPV) (m2.7.2 Section 3.2.9.1). Dose separation is not relevant for CAB LA, which is administered IM, because the interaction with oral CAB occurs in the GI tract. The impact of the Phase III dose separation strategy was not evaluated in a separate PK study. Based on data with other INIs, administration of antacids containing divalent cations 4 hours after oral CAB is not expected to impact plasma CAB exposure; however, reduced plasma CAB exposure is expected when antacids containing polyvalent cations are administered 2 hours before oral CAB. Oral CAB 30 mg once daily is the recommended dose for the OLI. Because oral CAB 10 mg once daily (67% of 30 mg dose) demonstrated efficacy in both induction and maintenance of virologic suppression, a reduction in plasma CAB exposure when antacids containing polyvalent cations are administered 2 hours before oral CAB 30 mg is not expected to be clinically relevant during the 1-month OLI or during oral bridging (up to 2 months). No dose separation is required with mineral supplements, such as calcium and iron, because the reduction in plasma CAB exposure is not expected to be clinically relevant based on magnitude of reduction observed for other INIs.

3.4.1.4. CAB Dose Recommendations with Transporter Inhibitors

In vitro, CAB is a Pgp and BCRP substrate, but because of its high permeability, no alteration in absorption is expected when co-administered with either Pgp or BCRP inhibitors (m2.7.2 Section 3.2.9.1).

3.4.2. Effect of CAB on the PK of Coadministered Drugs

Based on clinical drug interaction, PBPK modelling, mechanistic static modelling, and in vitro data, no clinical drug interaction risk was identified for co-administrated substrates of drug metabolizing enzymes CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 3A, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17 and substrates of drug transporters Pgp, BCRP, BSEP, MRP2, OCT1, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2K, MRP4, and OCT2 (Table 7). Additional details of the modelling and analyses conducted are presented in m2.7.2 Section 3.2.9.2.

Table 7 Effect of CAB on the Pharmacokinetics of Concomitant Medications

Concomitant Drug Regimen		N	Oral CAB Regimen	Geometric Mean Ratio (90% CI) of Co-administered drug PK parameters with/without CAB No Effect = 1.00			Study	Clinical Recommendation
				Ctau	AUC(0-tau)	Cmax		
MDZ 3 mg Single Dose		12	30 mg Once daily	ND	1.10 (0.95, 1.26)	1.09 (0.94, 1.26)	LAI116815	No dose adjustment
RPV 25 mg Once Daily		11	30 mg Once daily	0.92 (0.79, 1.07)	0.99 (0.89, 1.09)	0.96 (0.85, 1.09)	LAI116181	No dose adjustment
LNG/EE Once Daily	LNG 0.15 mg	19	30 mg Once daily	1.07 (1.01, 1.15)	1.12 (1.07, 1.18)	1.05 (0.959, 1.15)	LAI117011	No dose adjustment
	EE 0.03 mg			1.00 (0.919, 1.10)	1.02 (0.968, 1.08)	0.922 (0.827, 1.03)		

Data Source: m2.7.2 In-text Table 115.

3.4.2.1. Dose Recommendations for OAT1 and OAT3 Substrates When Co-administered with CAB

No dose adjustment is required when CAB is co-administered with OAT1/3 substrates, including sensitive substrates with narrow therapeutic indices, such as methotrexate (m2.7.2 Section 3.2.9.2). CAB is not a clinically relevant inhibitor of OAT1/3 based on mechanistic static and PBPK modeling and the renal safety data for oral CAB in combination with the sensitive OAT1/3 substrate TDF.

In the oral CAB Phase II Study LAI116482, 149/243 (61%) of subjects received TDF/FTC as background NRTIs at the start of the study and 94/243 (39%) received ABC/3TC (m2.7.2 Section 3.2.9.2). Overall rates of graded renal safety lab abnormalities were similar between oral CAB and EFV regimens and there were no graded CRCL abnormalities in any treatment group.

3.4.2.2. Dose Recommendations for CYP3A Substrates When Co-administered with CAB

No dose adjustment is required when CAB is co-administered with CYP3A substrates (m2.7.2 Section 3.2.9.2). A clinical drug interaction study demonstrated that CAB is not a CYP3A inhibitor or inducer because co-administration of oral CAB 30 mg once daily did not impact plasma MDZ (sensitive CYP3A substrate) exposure (Table 7).

3.4.2.3. Dose Recommendation for Hormonal Contraceptives

No dose adjustment is required when CAB is co-administered with progestin- and estrogen-containing contraceptives because oral CAB did not impact plasma LNG or EE exposures (Table 7) (m2.7.2 Section 3.2.9.2).

3.4.2.4. Dose Recommendations for ARV Medications

In a clinical drug interaction study, CAB had no impact on plasma RPV exposure and RPV had no impact on plasma CAB exposure (Table 6, Table 7); these data supported co-administration of CAB + RPV in clinical safety and efficacy studies (m2.7.2 Section 3.2.9.2).

Alternative HAART should be initiated as soon as feasible, no later than one month following discontinuation of CAB + RPV monthly regimen and no later than 2 months following discontinuation of the CAB + RPV every 2 months regimen, to maintain suppression of viral load and to reduce the chance of any CAB resistance emerging while CAB concentrations are waning (m2.7.2 Section 3.1.5). Based on the in vitro and clinical drug interaction profile, CAB is not expected to alter concentrations of other ARV medications including PIs, NNRTIs, NRTIs, INIs, entry inhibitors, and ibalizumab.

3.5. Pharmacodynamics

The pharmacodynamic studies are described in m2.7.2 Section 2.6.2.

Supratherapeutic concentrations did not prolong QTc interval following oral CAB administration. Proposed commercial doses of oral CAB and CAB LA do not prolong the QTc interval.

In Study LAI117009 (TQT study), a supratherapeutic dose of oral CAB 150 mg Q12h x 3 doses had no effect on cardiac repolarization, there was no relationship between plasma CAB concentrations and ddQTcF, and there were no other safety findings with this regimen (m2.7.2 Section 2.6.2).

3.6. Pharmacokinetic-Pharmacodynamic Relationships

3.6.1. PK/PD Efficacy Relationship

In the pooled analysis of Study 201584 and Study 201585, as well as in Study 207966, the rate of CVF was low, less than 2% across all treatment groups at Week 48 (pooled Studies 201584 and 201585 and Study 207966; Section 4.6.2.3). For subjects with CVF, CAB and RPV plasma concentrations at the SVF visit overlapped with plasma concentrations of subjects with HIV-RNA <50 c/mL at the corresponding visit, making it difficult to establish a causal relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure (Section 4.6.2.3 and Section 4.9). In Study 201584, Study 201585, and Study 207966, CAB and RPV concentration-time profiles for subjects with snapshot HIV-1 RNA ≥50 c/mL at Week 48 (n=25 across studies) were generally below the observed median while the majority were within the 5th and 95th percentile of observed data for the remainder of the population (n=1611 across three studies) (m2.7.2 Section 2.1.4).

3.6.2. PK/PD Safety Relationship

PK/PD analyses following oral and LA CAB administration did not identify an association between plasma exposure and any safety parameter (m2.7.4 Section 5.5).

3.6.3. Univariable and Multivariable Logistic Regression Analysis

In Study 207966, univariable and multivariable logistic regression analyses (using backward covariate selection of predictors that were significant in the univariable analysis with $p < 0.15$) were conducted for the population without prior exposure to CAB + RPV and for the overall population (m2.7.2 Section 2.1.2.1). The following factors were evaluated: treatment (dosing regimen), age, race, sex, Baseline CD4+ cell count, Baseline HIV-1 RNA, derived Baseline CDC Stage, Baseline BMI, Baseline third agent class, Week 8 RPV pre-dose concentration, Week 8 CAB pre-dose concentration, length of first RPV injection needle, and length of first CAB injection needle.

In both the univariable and multivariable regression analyses for the overall population, Baseline CDC stage of disease, Baseline BMI, and Week 8 CAB plasma concentration at the end of the dosing interval following the first injection were identified as statistically significant predictors of having a Week-48 HIV RNA ≥50 c/mL.

In the univariable regression analysis for subjects without prior exposure, Baseline BMI, and Week 8 CAB plasma concentration (at the end of the dosing interval following the first injection) were identified as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL (m2.7.2 Section 2.1.2.1). In the multivariable analysis for subjects without prior exposure, only BMI (>30 kg/m^2) was retained as a statistically significant predictor of Week 48 HIV RNA ≥50 c/mL (Odds Ratio [95% CI; (p-value)] 5.626 [1.48, 21.4 (0.011)]), without accounting for multiplicity.

Not all factors, inclusive of pre-existing resistance mutations and PK levels at time of failure, were considered in this model, limiting interpretation.

To address these limitations, subsequent multivariable and baseline factors analyses including additional potential covariates were conducted using pooled data from Studies 201584, 201585, and 207966, and these findings are summarized in Section 3.6.4 and Section 4.9.

3.6.4. Multivariable Analyses of Viral Factors and Subject Characteristics, Dosage Regimen, and Plasma Drug Concentrations with Virologic Outcome Across Phase III/IIIb Studies 201584, 201585, and 207966

A MVA was performed on the pooled Phase III/IIIb studies (201584, 201585, and 207966), which included data from 1039 HIV-infected adults with no prior exposure to CAB + RPV to explore potential predictors of virologic outcomes through Week 48 in the pooled CAB LA + RPV LA treatment group [GSK Doc. No. 2020N452718_01]. Results of the analyses showed that CVF is an infrequent multifactorial event, with a rate of ~1% in the LA arms across 3 Phase III studies (201584, 201585, and 207966) through Week 48. RPV Ctrough, archived RPV RAMs at Baseline (per PBMC-based HIV-1 DNA sequencing), HIV-1 Subtype A6/A1, and high BMI (≥30 kg/m^2) had a statistically significant association with virologic failure. However, regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%), thus limiting the predictive value of these factors, particularly in isolation. Additional details about the MVA and Baseline factors analyses are provided in Section 4.9. A full summary of the analysis is provided in m2.7.2 Section 3.1.1.3. Virology results are presented in m2.7.2.4.

3.7. Clinical Pharmacology Conclusions

The proposed monthly and every 2 months CAB regimens achieve plasma concentrations similar to those from efficacious oral CAB 10 mg and 30 mg once daily doses. The following conclusions apply to the CAB + RPV regimen.

- CAB LA + RPV LA is a complete ARV regimen; the safety and efficacy of the proposed monthly regimen was established in 2 Phase III studies (201584 and 201585) and the safety and efficacy of the proposed every 2 months regimen was established in the Phase IIIb Study 207966.
    - The proposed CAB monthly regimen is oral CAB 30 mg once daily for 1 month followed by an initial dose of CAB LA 600 mg IM and subsequent monthly doses of CAB LA 400 mg IM, administered with the proposed RPV monthly regimen.
    - The proposed CAB every 2 months regimen is oral CAB 30 mg once daily for 1 month followed by 2 initial dose of CAB LA 600 mg IM 1 month apart and

subsequent doses every 2 months of CAB LA 600 mg IM when administered with the proposed every 2 months RPV regimen in HIV-infected individuals.

- The rate of CVF in subjects in individual studies 201584, 201585, and 207966 receiving the Q4W or Q8W regimen was low, and overlapping plasma CAB and RPV concentrations in subjects with CVF vs. subjects with HIV-RNA <50 c/mL made it difficult to establish a relationship between plasma concentration and the occurrence of virologic failure. Multiple factors, including plasma concentrations and viral phenotype, may be associated with the occurrence of virologic failure.
- CVF is an infrequent multifactorial event, with a rate of ~1% in the LA arms across 3 Phase III studies (201584, 201585, and 207966) through Week 48.
- In an MVA using data pooled from Phase III/IIIb studies (201584, 201585, 207966), RPV Ctrough, archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and high BMI (≥30 kg/m^2) had a statistically significant association with virologic failure. However, regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%), and no Baseline factor when present in isolation was predictive of virologic failure.
- No relationships between plasma CAB concentrations and safety parameters of interest were identified in the CAB + RPV Phase III/IIIb studies.
- CAB may be administered without dose adjustment in patients with mild and moderate HI (Child-Pugh A and B); CAB has not been studies in patients with severe hepatic impairment. CAB may be administered without dose adjustment in patients with mild to severe renal impairment who did not require renal replacement therapy, and regardless of age (≥18 years of age), gender, race, body size (weight, BMI), smoker status, or UGT1A1 polymorphism.
- Drug Interactions Requiring Contraindication with CAB:
  - Metabolism: UGT1A1 and/or CYP3A inducers RIF, RBT (CAB LA in combination with RPV LA), rifapentine, CBZ, oxcarbazepine, phenobarbital, and phenytoin.
- Because absorption is prolonged following IM administration of CAB LA, CAB can be detected in plasma for more than a year in some individuals. Alternative HAART should be initiated as soon as feasible and no later than 1 month following discontinuation of the monthly CAB LA regimen, or no later than 2 months following discontinuation of the every 2 months CAB LA regimen, to maintain suppression of viral load and so reduce the chance of any CAB resistance emerging while concentrations are waning.

4. OVERVIEW OF EFFICACY

The pivotal studies supporting the efficacy of CAB injection, in combination with RPV injection, for the treatment of HIV-1 are Phase III Study 201584, Study 201585, and Phase IIIb Study 207966. Results from these studies indicate that the monthly CAB + RPV dosing regimen is non-inferior to standard of care and the every 2 months dosing regimen is non-inferior to the monthly dosing regimen for the treatment of HIV-1

infection in adults with no known or suspected resistance to CAB or RPV. A detailed summary of clinical efficacy is presented in m2.7.3.

4.1. Rationale for Dose Selection in Clinical Development

The proposed commercial dosing regimens for CAB + RPV (Table 3) were used in Study 201584 (monthly), Study 201585 (monthly), and in Study 207966 (monthly and every 2 months). The CAB doses for Phase III/ IIIb were selected on the basis of 2 Phase IIb trials (Study LAI116482 for oral CAB and Study 200056 for CAB LA).

4.1.1. CAB Oral

An OLI of CAB 30 mg + RPV 25 mg was included in Study 201584, Study 201585, and Study 207966 to evaluate the potential in each subject for ADRs that would preclude IM dosing. The same oral CAB and RPV doses were used for periods of oral therapy to cover planned missed IM injections.

CAB dose selection was initially informed by Phase IIa oral dose-ranging studies evaluating the short-term antiviral activity of CAB monotherapy at 5 mg and 30 mg/day where significant reductions in plasma HIV-1 RNA from Baseline were observed (mean decrease of >2.1 log10 c/mL on Day 11) (m2.7.3 Section 4.1.1.2). Thereafter, Phase IIb Study LAI116482 was conducted to support dose selection of oral CAB (10, 30, or 60 mg once daily) for inducing virologic suppression in combination with 2 NRTIs and secondly, by confirming durability of dose-response for maintaining virologic suppression following switch to dual treatment with oral CAB + RPV 25 mg once daily (m2.7.3 Section 4.1.1.1). All oral doses of CAB achieved durable suppression of HIV infection with a 2-drug (CAB + RPV) maintenance regimen, and CAB was well tolerated across all doses studied. A differentiated dose-response relationship among the 3 CAB doses was not observed given a high proportion of subjects across CAB dose levels achieved virologic suppression with plasma HIV-1 RNA <50 c/mL compared with the EFV + 2 NRTI control group at Week 24. On this basis, CAB 30 mg once daily was selected as OLI for Study 200056, Study 201584, Study 201585, and Study 207966 based on PK, safety, and efficacy results in Study LAI116482.

4.1.2. CAB LA

Study 200056 was a Phase IIb clinical study conducted to support dose selection of IM CAB LA + RPV LA for the maintenance of virologic suppression. The Phase II dose selection strategy for CAB LA was based on maintaining efficacious plasma CAB concentrations beginning with the first injections and throughout the course of therapy. Initial and steady-state exposures of CAB following IM injection were predicted based on population PK modeling of healthy and HIV-infected subject data and supported by the lack of drug-drug interaction between CAB and RPV following concomitant administration.

The dose and dosing frequency of CAB LA was based on maintaining plasma concentrations at the end of a dosing interval at or above mean exposures following the

efficacious 10 mg oral dose observed in Study LAI116482 (m2.7.3 Section 4.1.1.1). A higher initiation dose was chosen to quickly achieve target concentrations with a lower continuation dose that was predicted to achieve steady-state mean CAB plasma concentrations ≥1.35 μg/mL (target) in 99.6% and ≥80% of subjects following Q4W and Q8W dosing, respectively (m2.7.3 Section 4.1.2.3).

Both CAB LA + RPV LA Q4W and Q8W regimens demonstrated high and comparable rates of viral suppression compared with oral CAB + 2 NRTI in Study 200056 at Week 32 and Week 48 (m2.7.3 Section 4.1.2.3). However, a higher rate of virologic non-response of 7% in the Q8W group compared with <1% in the Q4W group was observed at Week 48. Plasma CAB geometric mean trough concentrations for both Q4W and Q8W regimens remained between the geometric mean Cτ values of 10 mg and 30 mg once daily.

Results from Study 200056 through Week 48 supported progression of the Q4W dosing regimen with maintenance doses of CAB LA 400 mg IM + CAB LA 600 mg IM in Phase III studies based on lower virologic non-response rates and similar safety to the Q8W dosing group (m2.7.3 Section 4.1.2.3). Using population PK modelling, the initiation dose strategy was optimized for Phase III studies to simplify and align the number of injections at each dosing visit and to achieve earlier attainment of target RPV exposures following the initial injection without impacting steady-state drug levels (GSK Document Number 2017N345267_00 and GSK Document Number 2018N370336_00). CAB LA initiation dose was decreased from 800 mg to 600 mg effectively decreasing the number of injections and injection volume from two-2 mL injections to a single 3 mL IM injection. This change was predicted to maintain mean plasma CAB concentrations comparable to the 10 mg oral dose during the early phase.

Q8W dosing of CAB + RPV has been evaluated in the ongoing Phase IIIb Study 207966 [GSK Document No. 2019N406358_01]. The selected doses and dosing regimen of CAB LA used for Q8W and Q4W dosing, in combination with RPV LA, were selected based on the Week 96 results from Phase IIb Study 200056 (m2.7.3 Section 4.1.2.3). Additional details around Q8W dose optimization are discussed in m2.7.2 Section 3.1.1.2 and in the Study 207966 protocol.

4.2. Clinical Trial Methodology and Design

Both Phase III, ongoing, pivotal efficacy trials, Study 201584 and Study 201585, are randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials evaluating the monthly CAB + RPV dosing regimen compared with standard of care (Table 1). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

The Phase IIIb Study 207966 is an ongoing, randomized, multicenter, parallel-group, open-label, non-inferiority trial evaluating the monthly CAB + RPV dosing regimen compared with the every 2 months dosing regimen (Table 1). The majority of subjects in Study 207966 were enrolled from the ongoing Phase III Study 201585. The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

4.3. Selection of Patient Populations

In Studies 201584, 201585, and 207966, HIV-1 infected subjects with any evidence of primary resistance based on the presence of any known major INSTI or NNRTI resistance-associated mutation, except for K103N, were excluded.

4.3.1. Study 201584

Study 201584 enrolled HIV-1 infected, ARV treatment-naïve subjects who achieved virologic suppression (<50 c/mL) after 20 weeks of induction therapy with ABC/DTG/3TC (or DTG + 2 NRTIs if HLA-B*5701 positive). Subjects were then randomized on Day 1 to either continue CAR (ABC/DTG/3TC) or switch to LA therapy. Subjects randomized to the LA group would proceed with 4 weeks of CAB + RPV OLI before receiving Q4W CAB + RPV.

4.3.2. Study 201585

Study 201585 enrolled HIV-1 infected, virologically suppressed (>6 months prior to Screening) subjects without history of virologic failure on uninterrupted first or second CAR regimen (ie, 2 NRTIs plus an INI, NNRTI, or PI). Median [range] treatment duration prior to enrollment was 4.3 [0.6 - 21.4] years (GSK Document Number 2018N370336_00 Data Source Table 1.31). Subjects were then randomized on Day 1 to either continue CAR or switch to LA therapy. Subjects randomized to the LA group would proceed with 4 weeks of CAB + RPV OLI before receiving Q4W CAB + RPV.

4.3.3. Study 207966

Study 207966 enrolled HIV-1 infected, virologically suppressed (>6 months prior to Screening) subjects on stable ART including subjects who completed, at minimum, Week 52 of Study 201585 (GSK Document Number. 2019N406358_01). In addition to subjects rolled over from Study 201585, additional subjects on SOC treatment were screened to supplement enrollment such that the study could be appropriately statistically powered. Subjects received 4 weeks of CAB + RPV OLI and then transitioned to either monthly or every 2 months CAB + RPV LA dosing regimen.

4.4. Efficacy Endpoints and Statistical Considerations of Efficacy Analyses

In Studies 201584, 201585, and 207966, the primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (i.e., virologic failure) at Week 48 using the Snapshot algorithm. Additional efficacy endpoints are described in m2.7.3 Section 1.5.

Efficacy analyses were performed for the ITT-E population, which consisted of all randomly assigned subjects who received at least 1 dose of study drug. Sensitivity analyses of the primary efficacy endpoint were conducted based on the PP population.

Standard analysis methods were applied (m2.7.3 Section 1.6). Stratification factors applied at randomization were induction Baseline HIV-1 RNA and sex at birth for Study 201584, and maintenance Baseline third agent class and sex at birth for Study 201585. In Study 207966, subjects were stratified at randomization by prior CAB + RPV exposure: 0 weeks, 1-24 weeks, >24 weeks.

4.5. Subject Disposition and Baseline Characteristics

In the pooled analysis of Study 201584 and Study 201585 through Week 48, a total of 591 subjects were randomized and treated with CAB + RPV and 591 subjects were randomized and treated with CAR (m2.7.3 Section 3.1). Similar proportions of subjects in each treatment group withdrew from the trial (CAB + RPV: 9%; CAR: 7%) (m2.7.3 Section 3.2). The most common reasons for withdrawal were AE (CAB + RPV: 4%; CAR: 2%) and withdrew consent (CAB + RPV: 1%; CAR: 2%).

In Study 207966, a total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W: 524 subjects; Q4W: 525 subjects) (m2.7.3 Section 3.1). Of these, 253 subjects (Q8W, 126 subjects; Q4W, 127 subjects) enrolled from the Q4W group of Study 201585 and 4 subjects (2 in each group) were randomized but not treated. Similar proportions of subjects in each treatment group withdrew from the trial (Q8W: 7%; Q4W: 8%) (m2.7.3 Section 3.2). The most common reasons for withdrawal were AE (Q8W: 2%; Q4W: 2%) and withdrew consent (Q8W: 1%; Q4W: 4%).

Demographic and Baseline characteristics were similar across treatment groups in Studies 201584 and 201585 (m2.7.3 Section 3.3). Of note, 27% and 28% of subjects were women in the pooled analysis in the CAB + RPV and CAR groups, respectively. Further, 17% and 21% of subjects were 50 years of age or older in the pooled analysis in the CAB + RPV and CAR groups, respectively.

In Study 207966, demographic and Baseline characteristics were generally similar between the 2 treatment groups (m2.7.3 Section 3.3). Although the majority of subjects were male, the study enrolled 27% females (sex at birth). Almost half (46%) of all subjects were ages 35 to <50 years, with a median (range) of 42 (19 to 83) years. Further, 27% of subjects were ≥50 years of age in both the Q4W and Q8W groups.

Additional details of Baseline characteristics for each study are presented in m2.7.3 Section 3.3.2.

4.6. Efficacy Results

4.6.1. Primary Efficacy Results

In the pooled analysis of Studies 201584 and 201585 using a pre-specified non-inferiority margin of -4%, once-monthly CAB + RPV is non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects, with <2% of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot algorithm (adjusted difference 0.2 [-1.4, 1.7], Table 8). Primary endpoint results were consistent between Study 201584 and

Study 201585, allowing both study data sets to be pooled and subgroup analyses to be based upon the pooled data set.

Treatment differences between CAB + RPV and CAR in the rates of HIV-1 RNA ≥50 c/mL per Snapshot were consistent between Study 201584 and Study 201585, suggesting that the duration of CAR treatment prior to the initiation of monthly CAB + RPV does not impact the overall virologic failure rates (m2.7.3 Section 3.4.1).

Longer term data from the Week 96 analysis of Study 201584 support the durability of the CAB + RPV regimen (m2.7.3 Section 5.1). The secondary efficacy analyses demonstrated that once monthly CAB + RPV continued to be non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects at Week 96, with few subjects (3.2% in each treatment group) having plasma HIV-1 RNA ≥50 c/mL at Week 96 (ITT-E and PP). The majority of subjects remained suppressed with HIV-1 RNA <50 c/mL at Week 96 via Snapshot analysis (86.6%, CAB + RPV; 89.4%, CAR).

In Study 207966, The primary efficacy analysis demonstrated that CAB LA + RPV LA every 2 months dosing regimen was non-inferior to CAB LA + RPV LA monthly dosing regimen in maintaining virologic suppression in HIV-1 infected subjects at Week 48, with <2% of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot algorithm in either group for the ITT-E population (m2.7.3 Section 3.4.1). The upper bound of 95% CI for the adjusted treatment difference between Q8W and Q4W was 2.2%, which was less than the pre-defined non-inferiority margin of 4%. (Table 8). Results for the PP population were similar to those for the ITT-E population (m2.7.3 Section 3.4.1).

Table 8 Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, Pooled Data (201584 and 201585), and Study 207966 (ITT-E Populations)

Treatment [a]	Number of Failures/ Total Assessed (%)	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV Q4W	6/283 (2.1)	-0.4 (-2.8, 2.1)	-0.4 (-2.8, 2.1)
CAR	7/283 (2.5)		
201585			
CAB + RPV Q4W	5/308 (1.6)	0.7 (-1.1, 2.4)	0.7 (-1.2, 2.5)
CAR	3/308 (1.0)		
Pooled Studies 201584 and 201585			
CAB + RPV Q4W	11/591 (1.9)	0.2 (-1.3, 1.7)	0.2 (-1.4, 1.7)
CAR	10/591 (1.7)		
Study 207966			
CAB + RPV Q8W	9/522 (1.7)	0.8 (-0.6, 2.2)	0.8 (-0.6, 2.2)
CAB + RPV Q4W	5/523 (1.0)		

Data Source: ISE/ISS Table 2.01, GSK Document Number. 2019N406358_01 Table 2.1.

a. In the Data Source tables, for Study 201584, CAR = ABC/DTG/3TC.

b. For Pooled Data: Difference: Proportion on CAB + RPV (Q4W IM) – Proportion on Control (unadjusted). For Study 207966: Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W

c. Based on CMH stratified analysis adjusting to Baseline viral load and Gender for Study 201584; adjusting to 3rd ART class and Gender for Study 201585; and adjusting to 10 strata for pooled analysis. For Study 207966: based on CMH stratified analysis adjusting for Baseline stratification factor of prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

4.6.1.1. Subgroup Analysis of the Primary Endpoint: Subjects with Plasma HIV-1 RNA ≥50 c/mL

To assess the generalizability of the primary analysis results, consistency of the treatment difference was explored within subgroups. One-way homogeneity across the levels of each variable used to stratify randomization was tested. In addition, potential treatment-by-subgroup interactions were evaluated via the assessment of summaries of the treatment differences across subgroups (i.e., age, race, country, Baseline CD4+ group, Baseline CDC Stage).

In each of the Phase III studies (201584 and 201585) and in the pooled analysis of both studies, there were no meaningful differences between treatment groups observed for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL when analyzed by subgroup and there were no statistically significant differences in treatment effect between the two groups in any subgroup analyses (m2.7.3 Section 3.4.1.1.1). A consistent showing of non-significant tests of homogeneity across randomization strata (p-value ≥0.10), were observed, supporting the overall primary endpoint conclusion of non-inferiority.

In Study 207966, 9/522 (1.7%) subjects in the Q8W group and 5/523 (1%) subjects in the Q4W group had HIV-1 RNA ≥50 c/mL at Week 48 (m2.7.3 Section 3.4.1). Within each randomization strata (prior exposure to CAB + RPV), the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm) was similar between treatment groups (m2.7.3 Section 3.4.1.1.2). The proportion of Q8W subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm) was similar between those with no prior exposure to CAB + RPV (1.5%) and those with prior exposure to CAB + RPV (2.1%). Within the Q4W group, no subjects previously treated with CAB + RPV and 1.5% of subjects with no prior exposure to CAB + RPV had HIV RNA ≥50 c/mL at Week 48.

The relatively small number of events limits the ability to make a robust conclusion regarding subgroup analyses in Study 207966. Treatment differences for the primary endpoint (proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm) were generally consistent across the strata within the following subgroups: demographic factors (age, gender, race, BMI), Baseline CDC stage of disease, Baseline viral load, Baseline CD4+ lymphocyte count, and participating countries (m2.7.3 Section 2.3). The proportion of Snapshot virologic failures was numerically higher in the Q8W arm compared with the Q4W arm in female subjects (5/137 [3.6%] and 0/143 [0%] in females vs 4/385 [1.0%] and 5/380 [1.3%] in males, respectively) and in subjects with BMI ≥30 kg/m^2 (6/113 [5.3%] in the Q8W group and 2/98 [2.0%] in the Q4W group for BMI ≥30 kg/m^2 vs 3/409 [0.7%] in the Q8W group and 3/425 [0.7%] in the Q4W group for BMI <30 kg/m^2). These differences in proportions are not considered clinically relevant.

4.6.2. Secondary Efficacy Results

4.6.2.1. Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis)

In the pooled analysis (Study 201584 and Study 201585), high rates of plasma HIV-1 RNA <50 c/mL were observed in both treatment groups (Table 9) meeting the definition of non-inferiority (lower bound above -10%) (m2.7.3 Section 3.4.2.1). These results are consistent with the conclusions drawn from the primary efficacy analysis.

In Study 207966, at Week 48, the majority of subjects in both treatment groups in the ITT-E Population remained suppressed (plasma HIV-1 RNA <50 c/mL: Q8W, 94%; Q4W, 93%), and the non-inferiority criterion was met for this secondary endpoint (Table 9). Results for the PP Population were consistent with those for the ITT-E Population. These results are consistent with the conclusions drawn from the primary efficacy analysis.

Table 9 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, Pooled Data (201584 and 201585), and Study 207966 (ITT-E Populations)

Treatment	Number Responded[a]/ Total Assessed	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV	265/283 (94)	0.4 (-3.7, 4.4)	0.4 (-3.7, 4.5)
CAR	264/283 (93)		
201585			
CAB + RPV	285/308 (93)	-2.9 (-6.7, 0.8)	-3.0 (-6.7, 0.7)
CAR	294/308 (95)		
Pooled Studies 201584 and 201585			
CAB + RPV	550 / 591 (93)	-1.4 (-4.1, 1.4)	-1.4 (-4.1, 1.4)
CAR	558 / 591 (94)		
P-value for Test of Homogeneity[d]			0.765
Study 207966			
CAB + RPV Q8W	492/522 (94)	0.8 (-2.2, 3.7)	0.8 (-2.1, 3.7)
CAB + RPV Q4W	489/523 (93)		

Data Source: ISS/ISE Table 2.08; GSK Document Number. 2019N406358_01 Table 2.8.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

a. Number Responded = Number of subjects with HIV-1 RNA <50 c/mL.
b. For Studies 201584 and 201585, Difference: Proportion on CAB + RPV (Q4W IM) – Control (unadjusted). For Study 207966, Difference: Proportion on Q8W – Proportion on Q4W.
c. Based on Cochran-Mantel Haenszel stratified analyses adjusting to Baseline viral load and sex at birth for Study 201584; adjusting to 3rd ART class and sex at birth for Study 201585; and adjusting to 10 strata for pooled analysis. For Study 207966, Based on CMH stratified analysis adjusting for prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).
d. One-sided p-value from weighted least squares statistic, across 10 randomization strata for pooled analysis.

Additional sensitivity analyses of the secondary efficacy endpoint of proportion of subjects with HIV-1 RNA <50 c/mL are described in m2.7.3 Section 3.4.2.1.1 (by randomization strata) and Section 3.4.2.1.2 (by visit). Results for the sensitivity analyses were consistent with the overall results for each of the Phase III/IIIb studies.

4.6.2.2. Study Outcomes at Week 48: Snapshot Outcomes

Snapshot outcomes at Week 48 for Study 201584, Study 201585, the pooled analysis (201584 + 201585), and Study 207966 are shown in Table 10. Snapshot outcomes at Week 48 for subjects receiving the CAB + RPV Q4W regimen in Studies 201584 and 201585 (pooled data) are consistent with results observed in the CAB + RPV Q8W and Q4W treatment groups in Study 207966.

Table 10 Snapshot Outcomes at Week 48 for Study 201584, Study 201585, Pooled Data (201584 and 201585), and Study 207966 (ITT-E Populations)

Outcome	201584		201585		Pooled Data (201584 and 201585)		207966	
	CAB + RPV N=283 n (%)	CAR N=283 n (%)	CAB + RPV N=308 n (%)	CAR N=308 n (%)	CAB + RPV N=591 n (%)	CAR N=591 n (%)	CAB + RPV (Q8W) N=522 n (%)	CAB + RPV (Q4W) N=523 n(%)
HIV-1 RNA <50 c/mL	265 (93.6)	264 (93.3)	285 (92.5)	294 (95.5)	550 (93.1)	558 (94.4)	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL	6 (2.1)	7 (2.5)	5 (1.6)	3 (1.0)	11 (1.9)	10 (1.7)	9 (1.7)	5 (1.0)
Data in window not below threshold	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)	3 (0.5)	3 (0.5)	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	4 (1.4)	3 (1.1)	3 (1.0)	2 (0.6)	7 (1.2)	5 (0.8)	6 (1.1)	2 (0.4)
Discontinued for other reason while not below threshold	0	2 (0.7)	1 (0.3)	0	1 (0.2)	2 (0.3)	0	1 (0.2)
Change in background therapy	0	0	0	0	0	0	0	0
No Virologic Data	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)	21 (4.0)	29 (5.5)
Discontinued study due to AE or death	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)	9 (1.7)	13 (2.5)
Discontinued study for other reasons	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)	12 (2.3)	16 (3.1)
On study but missing data in window	0	0	0	0	0	0	0	0

Data Source: ISS/ISE Table 2.05; GSK Document Number. 2019N406358_01 Table 2.3.

Note: In the Data Source tables for Studies 201584 and 201585, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

4.6.2.3. Confirmed Virologic Failure at Week 48

CVF was defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. The details of viral resistance are presented in Section 4.9.

In the pooled analysis (Study 201584 and Study 201585), few subjects (7/591 [1.2%] subjects in both treatment groups) met CVF criteria through Week 48 (m2.7.3 Section 3.4.2.3). All subjects with CVF were offered a fully active oral ART regimen and consenting subjects were entered into LTFU. The majority (4/7) of subjects with CVF who entered LTFU were successfully re-suppressed after switching to an alternative oral ART regimen.

In Study 207966, the proportion of subjects with CVF through Week 48 (including subjects with dosing beyond Week 48) was 1.5% (8/522 subjects) for the Q8W group and 0.4% (2/523 subjects) for the Q4W group (m2.7.3 Section 3.4.2.3). All 10 subjects with CVF were offered a fully active oral ART regimen and entered into LTFU. 9/10 of the subjects with CVF who entered the LTFU study had HIV-1 RNA <50 c/mL at their last available visit [GSK Document Number 2019N406358_01 Listing 40].

4.7. Visits That Exceeded Injection Dosing Window

Oral therapy (CAB 30 mg + RPV 25 mg) is permitted to cover missed injection visits as per proposed labeling.

In Study 201584, a total of 47 injection visits for CAB + RPV subjects (out of 3577 total injection visits, representing 1.3%) were more than 7 days after the planned injection date (GSK Document Number 2017N345267_00 Data Source Table 3.6). Of these, 5 injection visits were more than 14 days after the planned injection visit. 1 subject in Study 201584 missed an injection visit without oral therapy.

In Study 201585, a total of 59 injection visits for CAB + RPV subjects (out of 3343 total injection visits, representing 1.8%) were more than 7 days after the planned injection date (GSK Document Number 2018N370336_00 Data Source Table 3.6). Of these, 5 injection visits were more than 14 days after the planned injection visit. No subjects missed an injection visit without oral therapy.

In Study 207966, some injection visits occurred more than 7 days after the planned injection visit (33/3719, representing <1.0% in Q8W; 58/7346, representing <1.0% in Q4W). No subjects missed an injection visit without oral therapy.

No cases of CVF were reported for subjects in any of the Phase III/IIIb studies who missed injection visits.

4.8. Oral Therapy

Oral therapy (CAB 30 mg + RPV 25 mg) is proposed to cover missed injection visits for a duration of up to 2 consecutive monthly missed injections (up to 3 months duration

between injections) or 1 every-2-months missed injection (up to 4 months duration between injections).

The overall efficacy and safety of oral CAB + RPV are supported by exposures across the CAB + RPV development program. A summary of the total exposure to oral CAB + RPV is presented in Table 11. The totality of the oral clinical data presented in Table 11 and the simulations discussed in m2.7.2 Section 3.1.4.1 support the use of oral therapy with CAB + RPV. When implemented as recommended, oral therapy should provide plasma CAB concentrations below safety thresholds. In an extreme case scenario where both oral CAB 30 mg once daily and CAB LA 400 mg Q4W are administered simultaneously under steady-state conditions, geometric mean Cmax is predicted to be 12.3 μg/mL, posing no safety concern.

Table 11 Summary of Exposure to Oral CAB 30 mg + Oral RPV 25 mg (Study 201584, Study 201585, Study 207966, Study 200056, Study LAI116482)

Treatment	# of Subjects	Person Time (years)
CAB 30 mg once daily oral	1909	1171
RPV 25 mg once daily oral [a]	1873	904

Data Source: 209552 Table 4.5.

Note: Person time was calculated up to the point of the subject's last dose administered or until 20DEC2018, except for Study 207966, which includes the full Week 48 data, for subjects still on treatment at that time.

a. For subjects that subsequently take oral therapy after starting LA, their time on oral therapy is also included in their total duration on oral.

In Studies 201584 and 201585 to Week 48, a total of 18 subjects received oral therapy for durations ranging from 3 days to approximately 2 months to cover missed injection(s) (m2.7.3 Section 3.6.2). All but 2 subjects resumed IM dosing. No cases of CVF were observed during oral therapy or following resumption of IM dosing.

In Study 207966 at Week 48, a total of 4 subjects in the Q8W group and 7 subjects in the Q4W group received oral therapy for durations ranging from 2 days to approximately 2 months (m2.7.3 Section 3.6.2).

In Study 200056 (Phase IIb), 8 subjects received oral therapy for a duration ranging from 17 to 56 days (m2.7.3 Section 3.6.2). All subjects were able to resume IM dosing and no cases of CVF were observed during a period of oral therapy or following resumption of IM dosing.

In addition to the use of oral therapy in Study 201584, Study 201585, Study 207966, and Study 200056, results from Study LAI116482 provide evidence for the safety and efficacy of oral CAB 30 mg + oral RPV 25 mg once daily for >2 years, supporting the use of oral therapy for an extended duration (GSK Document Number 2016N280049_00).

If a patient plans to miss a scheduled injection by more than 7 days, oral therapy (oral CAB 30 mg + oral RPV 25 mg once daily) should be used. Oral therapy is permitted to cover missed injection visits as per proposed labeling. Oral therapy should be initiated at

the time of the planned missed injection. Injection dosing should be resumed on the same day oral dosing completes, and as recommended in Table 12 and Table 13.

Table 12 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy for the Monthly CAB + RPV Dosing Regimen

Time Since Last Injection	Recommendation
≤2 months	Continue with monthly 2-mL injection dosing schedule as soon as possible.
>2 months	Re-initiate the patient on the 3-mL dose, and then continue to follow the monthly 2-mL injection dosing schedule.

Table 13 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy for the Every 2 Months CAB + RPV Dosing Regimen

Missed Injection Visit	Time Since Last Injection	Recommendation
Injection 2 (Month 3)	≤2 months	Resume with 3 mL (600 mg) injections as soon as possible and continue with the every 2 months injection dosing schedule.
	>2 months	Re-initiate the patient on the 3 mL (600 mg) dose, followed by a second 3-mL (600 mg) initiation injection one month later, then follow the every 2 months injection dosing schedule.
Injection 3 or later (Month 5 onward)	≤3 months	Resume with 3 mL (600 mg) injections as soon as possible and continue with the every 2 months injection dosing schedule.
	>3 months	Re-initiate the patient on the 3 mL (600 mg) dose, followed by a second 3-mL (600 mg) initiation injection one month later, then follow the every 2 months injection dosing schedule.

4.9. Multivariable and Baseline Factor Analyses of Virologic Outcome (Studies 201584, 201585, and 207966)

Multivariable and Baseline factor analyses were undertaken to examine the influence of Baseline viral factors and subject characteristics, dosage regimen, and post-Baseline plasma drug concentrations on CVF using regression modeling with a variable selection procedure.

For the primary analysis population, 1039 HIV-infected subjects were pooled from Phase III/IIIb Studies 201584, 201585, and 207966 (Week 48 analyses) who were naïve to CAB + RPV, eliminating previous exposure as a potential confounding factor. Subjects from Study 207966 who had transferred from the CAB + RPV arm of Study 201585 were excluded from this analysis. Of the 17 subjects from the 3 Phase III/IIIb studies who did not maintain virologic suppression through their first 48 weeks of CAB + RPV treatment and met CFV criteria, 4 were excluded from the analyses (3 due to prior exposure to

CAB + RPV in Study 201585 prior to transferring to Study 207966 and 1 due to CVF occurring prior to CAB + RPV injections in a subject who had oral lead-in therapy temporarily withheld during a work-up for a false positive pregnancy test). 13 (1.25%) of the 1039 subjects included in the MVA population met CVF criteria while receiving CAB + RPV (m2.7.3 Section 4.2.3).

A logistic regression model was used to examine the influence of 10 covariates known or suspected to contribute to virologic outcome, including drug PK and factors impacting drug exposure, key virus characteristics, and dosing interval (Q8W vs. Q4W) on the occurrence of CVF. Further details of the analysis population and the MVA and Baseline factor analysis methodology are provided in a separate report [GSK Document No. 2020N452718_01].

4.9.1. Results of Multivariable Analysis

Four of the examined covariates were significantly associated with increased risk of CVF ($p<0.05$ for each adjusted OR) (m2.7.3 Section 4.2.3):

- RPV RAMs at Baseline (determined through PBMC-based HIV-1 DNA sequencing in Study 201585 and Study 207966);
- HIV-1 Subtype A6/A1 (associated with integrase L74I polymorphism);
- RPV Ctrough 4 weeks following initial injection dose (per halving concentration);
- BMI (per unit increase in kg/m^2) (associated with CAB PK).

Overall, a high proportion of subjects (n=1531 [94%]) continued to maintain viral suppression in the Phase III/IIIb studies, thus limiting the predictive value of these identified covariates, particularly in isolation.

A significant association with CVF was not observed for the other 6 variables:

- Pre-specified INSTI mutation (excluding L74I non-M mixture) at Baseline
- NNRTI RAM(s) (excluding RPV RAMs) at Baseline
- Log2 of post hoc Week 8 CAB trough concentration
- L74I (non-M mixture) INSTI mutation at Baseline
- Female at birth
- Q8W regimen

Although the L74I polymorphism and CAB trough concentration at Week 8 did not significantly associate with CVF, they are correlated with factors that did have a significant association with CVF, specifically HIV Subtype A6/A1 and BMI, respectively.

Only 2 of 13 subjects with CVF had <2 factors associated with CVF; 46% of subjects (n=6) had 4 out of the following 5 factors: RPV PK ≤Q1, HIV-1 A6/A1, Baseline RPV RAMs, BMI ≥30 kg/ m^2, and CAB PK ≤Q1 (m2.7.3 Section 4.2.3).

Overall, the results of the MVA analysis indicate that no covariate alone is associated with a higher likelihood of experiencing CVF.

4.9.2. Results of Baseline Factor Analysis

In the Baseline factors analysis, the same covariates as in the MVA were explored, with the exception of PK parameters. Baseline archived RPV RAMs, HIV-1 Subtype A6/A1, and BMI ≥30 were selected ($p<0.05$) by the stepwise model selection procedure (m2.7.3 Section 4.2.3).

The majority of CVF cases (9 of 13; 69.2%) were multifactorial (≥2 Baseline factors present) [GSK Document No. 2020N452718_01]. The results of the Baseline factors analysis support the MVA findings and indicate that no Baseline factor alone is associated with a higher likelihood of developing CVF. In fact, even in the presence of 2 or more Baseline factors, 25/ 35 (71%) subjects maintained virologic suppression at Week 48 via the Snapshot algorithm. The CVF rate through Week 48 was <0.5% when 0 or 1 Baseline factor(s) were present.

4.10. Virology

CAB is an INI with an in vitro resistance profile similar to DTG. CAB retains activity against RAL single mutations Y143R, N155H, and Q148H, as does DTG. INI mutations Q148K and Q148R each cause approximately 5 FC increase to CAB while causing no increase in FC to DTG.

Across Study 201584 and Study 201585 through Week 48, CVF was observed in 1.2% (7/591) of subjects in the CAB + RPV group, and in 1.2% (7/591) of subjects in the CAR group (Section 4.6.2.3).

In Study 201584, 4 subjects in the CAB + RPV group and 4 subjects in the CAR group had CVF. Three CVFs in the CAB + RPV group had treatment emergent RPV and INI resistant mutations (m2.7.2.4 Section 4.2.1.2). All 3 had CAB resistance in vitro; 2 of the 3 had reduced in vitro RPV phenotypic susceptibility. All 3 were from Russia and had Subtype A1 virus; a total of 8 subjects with Subtype A1 were exposed to this regimen. The fourth CVF never received an injection and no treatment-emergent resistance mutations were observed. None of the 3 CVFs on CAR had treatment-emergent resistance mutations. No subjects met CVF between Week 48 and 96 in the CAB + RPV Q4W treatment group.

In Study 201585, CVF was rare (1%), with 3 subjects in the CAB + RPV group and 4 subjects in the CAR group. All 3 CVFs in the CAB + RPV group had RPV resistance mutations at the virologic failure timepoint. These RAMS were also present in the Baseline HIV-1 viral DNA for 2 the of the 3 subjects. These 3 subjects had Subtypes A, A1, and AG. One of the CVFs in the CAB + RPV group had INI resistance mutation,

N155H; this subject had a history of RAL use. No subjects met CVF criteria after Week 48.

In Study 207966, CVFs were infrequent in the study with 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm (m2.7.2.4 Section 4.2.1.4). Virus subtypes observed in CVF subjects were A or A1 (n=4), B (n=4) or C (n=2). RPV resistance-associated mutations were found in 5/10 CVF subjects in Baseline PBMCs and 7/10 subjects at SVF time point. At the SVF time point, in vitro phenotypic resistance to RPV occurred in 9/10 CVF subjects. INSTI resistance-associated mutations were present in 1/10 subjects in Baseline PBMCs and 7/9 subjects at SVF time point. At the SVF time point, in vitro phenotypic CAB resistance occurred in 4/8 CVF subjects. INSTI substitution, L74I, was present in 5 subjects at Baseline and 4 subjects at the SVF time points. No dolutegravir or bictegravir in vitro phenotypic resistance was observed in the CVF subjects.

The mutations associated with resistance to CAB LA, observed in the Phase IIb and Phase III studies, are E138K (n=1 Study 200056), G140R (n=1), Q148R (n=3, 1 of which came from Study 200056), and N155H (n=1) (m2.7.2.4 Section 4.2).

As a result of the prolonged release of CAB from depots after IM administration, plasma concentrations of CAB can be detected for more than a year in some subjects. Following discontinuation of CAB, to minimize the risk of developing viral resistance, it is essential to prescribe an alternative, fully suppressive ARV regimen, starting no later than 1 month after the final injection doses of CAB.

A summary of non-clinical and clinical virology can be found in m2.7.2.4 (Special Studies).

4.11. Health Outcomes

Subjects' views of their treatment were assessed with several patient reported outcome measures in Study 201584, Study 201585, and Study 207966. In order to compare the novel long-acting treatment regimen with the standard of care of daily oral ART, tolerability, and perception of the injections, as well as satisfaction and acceptance of the treatments were included as secondary outcome measures.

In the context of health outcomes, review of key subject demographic and clinical characteristics at Baseline demonstrates that subject populations are measurably different among the studies with regard to age, sex, time since diagnosis, and number of years on previous ART (m2.7.3 Section 3.3). Subjects in Study 201584 were naïve to treatment prior to enrolling in the study while those in Study 201585 had, on average, 5.6 years on their previous ART, and many subjects in Study 207966 were previously enrolled in Study 201585. These differences in subject population, especially regarding the length of time on prior oral ART, may be relevant factors to consider when interpreting health outcome data from the individual studies.

4.11.1. HIVTSQs and HIVTSQc

In Study 201585, the CAB + RPV group demonstrated a statistically significant and clinically meaningful improvement in total treatment satisfaction using HIVTSQs compared with the CAR group at each timepoint (m2.7.3 Section 3.7.1).

Baseline values for the HIVTSQs were higher in Study 201584 compared with Study 201585 and limit the possibility to show significant increase in mean difference between treatment groups (m2.7.3 Section 3.7.1). To account for this ceiling effect, the HIVTSQc change version was used at Week 48 for Study 201584 (m2.7.3 Section 3.7.2). The HIVTSQc assessed subjects' experience with their treatment at Week 48 compared with their treatment at Baseline. In Study 201584, subjects in the CAB + RPV group reported a statistically significant improvement in treatment satisfaction compared with subjects in the CAR group when compared with the Induction Phase.

In Study 207966, subjects reported very high levels of satisfaction with Q4W and Q8W dosing at Week 48 (m2.7.3 Section 3.7.1.2). For subjects with prior CAB + RPV exposure, Baseline treatment satisfaction (i.e. satisfaction with Q4W dosing) was high (approximately 62 out of possible 66 points in the HIVTSQs) and remained high across all time points, without significant differences between Q4W and Q8W dosing. For subjects without prior exposure to CAB + RPV, a significant increase from Baseline in treatment satisfaction was observed for both treatment groups at Weeks 24 and 48, statistically significantly favoring the Q8W group compared with the Q4W group (Week 24: p=0.036; Week 48: p=0.004). In the HIVTSQ change assessment, subjects with prior CAB + RPV exposure had high scores in both treatment groups at Week 48, with a statistically significant difference favoring the Q8W group (m2.7.3 Section 3.7.2.2). Similarly, in subjects without prior exposure to CAB + RPV, both groups had high HIVTSQc scores at Week 48, with a statistically significant difference favoring the Q8W group. These high rates of treatment satisfaction correlate with the low number of discontinuations in both study groups at Week 48 (Q8W, 7%; Q4W, 8%).

4.11.2. ACCEPT Scores (General Acceptance Domain)

In Study 201585, the CAB + RPV group demonstrated statistically significant improvements in treatment acceptance (based on the three-item General Acceptance domain), compared with the CAR group from Baseline to Week 44 (m2.7.3 Section 3.7.3.1). This difference was significant all timepoints for subjects on CAB + RPV in Study 201585. The high Baseline values observed in Study 201584 limit the opportunity for a significant increase in mean difference between treatment groups from Baseline to Week 44, indicating ceiling effects with this measure. Because subjects in Study 201585 had been receiving ART for approximately 5.4 years prior to participating in the study and those in Study 201584 were treatment-naïve, subjects from Study 201585 were more representative of the demands of HIV treatment over a long period of time.

In Study 207966, General Acceptance adjusted mean scores were similar in both treatment groups at Baseline and improved at Weeks 24 and 48, without any significant

difference between treatment groups and regardless of prior exposure to CAB + RPV (m2.7.3 Section 3.7.3.2).

4.11.3. Treatment Preference

Results from treatment preference assessments administered in the Phase III/IIIb studies indicated that the majority of subjects preferred CAB + RPV every 2 months dosing regimen over either the monthly dosing regimen or oral therapy (m2.7.3 Section 3.7.4). The most common reasons cited were frequency of administration and convenience in terms of ease to integrate into one's daily life.

4.12. Efficacy Conclusions

Comparisons across the 2 pivotal Phase III studies (Study 201584 and Study 201585), the pooled analysis at Week 48, and Phase IIIb Study 207966 show that:

- In Study 201584, Study 201585, and the pooled analysis, the primary efficacy analyses demonstrated that monthly dosing of CAB + RPV is non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E). The adjusted treatment difference between CAB + RPV and CAR for both studies and the pooled analysis met the non-inferiority criterion (upper bound of the 95% CI below 6% for the individual studies and below 4% for the pooled analysis).
- In Study 207966, the primary efficacy analysis demonstrated that the every 2 month dosing of CAB + RPV is non-inferior to the monthly dosing regimen of CAB + RPV on the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48. The adjusted treatment difference between Q8W and Q4W was 0.8 (95% CI –0.6, 2.2) which met the non-inferiority criterion, set below 4% for the primary endpoint (HIV-1 RNA ≥50 c/mL via Snapshot, ITT-E).
- In the ITT-E population (pooled data from Studies 201584 and 201585), the proportion of subjects with HIV-1 RNA ≥50 c/mL among subjects receiving Q4W treatment in the CAB + RPV group (11/591, 1.9%) was similar to the proportion of subjects with HIV-1 RNA ≥50 c/mL receiving CAB + RPV in the Q8W group (9/522, 1.7%) and Q4W group (5/523, 1%) in Study 207966.
- In Study 201584, Study 201585, and the pooled analysis, the key secondary efficacy analyses demonstrated that monthly dosing of CAB + RPV is non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E). Specifically, both studies and the pooled analysis established non-inferiority to comparator groups (CAR), with a non-inferiority margin of -10%. In Study 207966 at Week 48, 94% of Q8W CAB + RPV subjects and 93% of Q4W CAB + RPV subjects had plasma HIV-1 RNA <50 c/mL (ITT-E). The adjusted treatment difference between Q8W and Q4W was 0.8% (95% CI, -2.1%, 3.7%), which met the non-inferiority criterion for this secondary endpoint.
- At Week 48 for Studies 201584, 201585, and 207966, CVF was an infrequent (~1% across the 3 Phase III/IIIb studies) multifactorial event. Three Baseline factors

(archived RPV resistance mutations, A6/A1 subtype, and/or higher BMI [≥30 kg/m^2]), when found in combination (2 or more), represented an increased risk of CVF. When 0 or 1 Baseline factors were present, the Week 48 CVF rate was <0.5%.

- The results from Study 201584, Study 201585 and Study LAI116482 demonstrate that oral once-daily treatment with CAB 30 mg + RPV 25 mg is effective at maintaining virologic suppression prior to initiation of LA dosing. Further, these studies demonstrate that oral once-daily treatment with CAB 30 mg + RPV 25 mg can be successfully used for patients who require a temporary pause in LA dosing.
- The non-inferiority result established in Study 201584 and Study 201585 demonstrated that the length of HIV-1 RNA virologic suppression prior to initiation of CAB + RPV (i.e. <6 months or ≥6 months), did not impact overall response rates.
- In Study 201584, Study 201585, and the pooled analysis, the treatment effect (CAB + RPV vs. CAR) for the primary endpoint was consistent across the randomization stratification factors.
- The treatment effect (Q8W vs Q4W) for the primary endpoint in Study 207966 was consistent across randomization stratification factors of prior exposure to CAB + RPV, 0 weeks, 1-24 weeks, and >24 weeks), supporting the overall conclusions of non-inferiority in the primary and secondary endpoints.
- In the individual Phase III Studies 201584, Study 201585, the pooled analysis, and in Phase IIIb Study 207966, treatment differences within subgroups generally were consistent with the results of the overall analysis.
- In the pooled analysis of Study 201584 and Study 201585, the CAB + RPV group demonstrated greater improvement from Baseline in treatment satisfaction compared with the CAR group using the HIVTSQs. In Study 2076966, the CAB + RPV Q8W group without prior exposure to CAB + RPV demonstrated significantly greater improvement from Baseline in treatment satisfaction compared with the Q4W group using the HIVTSQs. Of respondents with prior exposure to CAB + RPV and randomized to the Q8W arm, preference for Q8W treatment was higher compared with Q4W or oral CAB + RPV; most common reasons were frequency of administration and convenience in terms of ease to integrate into one's daily life.
- Durability of the CAB + RPV LA regimen was demonstrated through 96 weeks in Phase III Study 201584 where once-monthly CAB + RPV continued to be non-inferior to oral CAR with respect to the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL and <50 c/mL at Week 96 (Snapshot Analysis).
- The CAB + RPV LA doses explored in the Phase 3 studies, both monthly and every 2 months dosing, generated statistically non-inferior outcomes against comparative regimens, with low overall HIV-1 RNA ≥50 c/mL event rates. No single identifiable factor, or combination of factors, was associated with a higher risk of an HIV-1 RNA ≥50 c/mL when evaluating individual subjects.

Overall, these results indicate that CAB, when used in combination with RPV as a monthly or every 2 months 2-drug regimen, is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. The long-acting injectable regimen dosed monthly is non-inferior to oral CAR without increased risk of virologic failure (HIV-1 RNA ≥50 c/mL),

and the long-acting, dosed every 2 months regimen is non-inferior to the monthly regimen. Overall, the monthly and every 2 months dosing regimens, enabling 6 to 12 injection visits per year, demonstrated no increased risk of virologic failure relative to comparator arms through Week 48.

5. OVERVIEW OF SAFETY

The safety profile of CAB + RPV in Phase II, III, and IIIb studies supports a favorable benefit-risk assessment for CAB in the indicated HIV-1 infected population.

For a full presentation of safety results, see the Clinical Summary of Safety (m2.7.4).

5.1. Introduction

An overview of study designs for the Phase II, III, and IIIb studies supporting the safety of CAB is presented in Section 4.2.

Exposure data for the CAB clinical program are provided in Section 5.1.3.

5.1.1. Data Cut-off Dates

Pooled data from Studies 201584 and 201585 Week 48 results that were reported through the LSLV cut-off date ([redacted] and [redacted], respectively) are presented. Additional safety data from the individual studies through Week 96 LSLV cut-off dates ([redacted] and [redacted], respectively) are also provided.

In Study 207966, all visits and assessments through Week 48 that occurred up to the LSLV cut-off date of [redacted] are included in the authorized clinical study database, and results are presented.

For the Phase II studies (LAI116482 and 200056), all visits and assessments through the end of study for Study LAI116482 (15 Jan 2019) and up to Week 160 (21 Jan 2018) for Study 200056 are included in the authorized clinical study database.

5.1.2. Population Included in Safety Analyses

The clinical trials used to support the safety of CAB are the 2 pivotal Phase III trials of CAB + RPV, Study 201584 and Study 201585, and the Phase IIIb Study 207966. Safety profiles of CAB and RPV were consistent across studies. All subjects who received at least 1 dose of study drug in these trials were included in the Safety Population or Extension Switch Population.

Additional safety information in HIV-1 infected subjects is presented from Phase II Studies LAI116482 (end of study) and 200056 (160 weeks).

5.1.3. Exposure in the Clinical Development Program

5.1.3.1. Phase III Studies

In the pooled analysis for Study 201584 and Study 201585 at Week 48, the median time of exposure of HIV-1 infected subjects to CAB + RPV was 382 days (54 weeks) (m2.7.4 Section 1.2.2). The median time of exposure of HIV-1 infected subjects to oral CAB + RPV from the OLI period of the Maintenance Phase (Week 48) of pooled Study 201584 and Study 201585 was 5.3 weeks.

At the Week 96 time point, subjects were exposed to CAB + RPV for at least 737 days (about 2 years) in Study 201584 and at least 911 days (about 2.5 years) in Study 201585 (m2.7.4 Section 1.2.3).

In Study 207966 (Week 48), the median time of exposure from Baseline to LA CAB + RPV was similar between treatment groups (Q8W, 447 days; Q4W, 445 days) (m2.7.4 Section 1.2.2). Subjects were exposed to LA CAB + RPV for a maximum of 1.5 years (582 days).

5.1.3.2. Phase II Studies

In Study 200056, the median number of CAB LA + RPV LA injections was 25 and 46 for the Q8W and Q4W treatment groups, respectively (m2.7.4 Section 1.2.4). The median number of injections was 11 and 20 for the optimized Q8W IM and optimized Q4W IM arms, respectively, during the Extension Period.

At the end of Study LAI116482, median exposure to oral CAB was 2179 days (311 weeks or almost 6 years) and median exposure to oral RPV was 2014 days (about 288 weeks or about 5.5 years) (m2.7.4 Section 1.2.4).

5.2. Non-Clinical Data Relevant to Human Safety

CAB and RPV are expected to be well tolerated as a two-drug regimen in patients, given the findings from the comprehensive packages of non-clinical testing of both agents, which suggest no overlapping toxicity. Non-clinical data are discussed in m2.7.4 Section 1.1.2 and a full analysis of the data is presented in m2.4 Section 5.

5.3. Safety in Clinical Pharmacology Studies

There were no safety findings in single dose or multiple dose trials with CAB LA in healthy volunteers that were different from those identified in trials in HIV-infected subjects (m2.7.4 Section 5.5).

The Phase I safety meta-analysis performed for CAB supports the favorable benefit-risk ratio for CAB (oral and LA) (m2.7.4 Section 5.5).

5.4. Adverse Events

With the exception of ISRs associated with IM CAB, safety results were similar for oral CAB, the monthly IM dosing regimen, and the every 2 months IM dosing regimen across the clinical development program. The occurrence of ISRs for the IM formulations reflects the method of administration. In all studies, very few ISRs led to withdrawal, and the frequency of ISR reporting decreased over time (Section 5.4.6.1). In Studies 207966 and 200056, 4 subjects were reported to have postinjection reactions; 3 cases apparently were related to injection with RPV (based on PK), which is administered at the same visit as CAB as part of the dosing regimen for HIV-1 treatment. The fourth case was not confirmed because a suitably timed post dose PK sample was not collected (Section 5.4.8).

An overall trend for greater frequency of drug-related AEs, including ISRs, was observed for CAB + RPV compared with CAR; however, there were few drug-related AEs that were Grade 3 to 5 AEs or SAEs (see Section 5.4.1.1 and Section 5.4.4, respectively). Within Study 207966, the proportions of subjects in the overview of AE categories were similar between the Q8W and Q4W groups. A summary of all AEs for Studies 201584, 201585, and 207966 (all Week 48 time points) is presented in Table 14 and non-ISR AEs are presented in Table 15. Phase II and long-term Phase III overall AEs were consistent with trends observed in Phase III/IIIb Week 48 results (m2.7.4 Section 2.1).

Table 14 Overview of All AEs in Studies 201584, 201585, Pooled 201584 + 201585, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Any AE	**267 (94)**	**225 (80)**	**294 (95)**	**220 (71)**	**561 (95)**	**445 (75)**	**473 (91)**	**482 (92)**
Any Grade 3/4/5 AE	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)	41 (8)	49 (9)
Any drug-related AE	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)	400 (77)	399 (76)
Any Grade 3/4/5 drug-related AE	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)	16 (3)	26 (5)
Any AEs leading to withdrawal	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)	12 (2)	13 (2)
Any SAE	**18 (6)**	**12 (4)**	**13 (4)**	**14 (5)**	**31 (5)**	**26 (4)**	**27 (5)**	**19 (4)**
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)	1 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0

Data Source: ISS/ISE Table 3.05; GSK Document Number. 2019N406358_01 in-text Table 25, Table 3.6, Table 3.13, Table 3.16, Table 3.19, Table 3.22, and Table 3.26.
Note: In the ISS Data Source tables, the CAB + RPV group is lited as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: Drug-related is based on investigator assessment.

Table 15 Overall Summary of Non-ISR AEs in Studies 201584, 201585, Pooled 201584 + 201585, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Any AE	**246 (87)**	**225 (80)**	**264 (86)**	**220 (71)**	**510 (86)**	**445 (75)**	**403 (77)**	**441 (84)**
Any Grade 3/4/5 AE	22 (8)	11 (4)	25 (8)	24 (8)	47 (8)	35 (6)	29 (6)	30 (6)
Any drug related AE	79 (28)	28 (10)	87 (28)	8 (3)	166 (28)	36 (6)	109 (21)	125 (24)
Any Grade 3/4/5 drug related AE	4 (1)	0	4 (1)	1 (<1)	8 (1)	1 (<1)	4 (<1)	5 (<1)
Any AEs leading to withdrawal	8 (3)	4 (1)	9 (3)	5 (2)	17 (3)	9 (2)	7 (1)	10 (2)[a]
Any SAE	**18 (6)**	**12 (4)**	**13 (4)**	**14 (5)**	**31 (5)**	**26 (4)**	**26 (5)**	**19 (4)**
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)	1 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0

Data Source: ISS/ISE Table 3.07; GSK Document Number. 2019N406358_01 Table 3.7, Table 3.14, Table 3.19, Listing 15, Listing 16, and Listing 17.

Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Note: Drug-related is based on investigator assessment.

[a]2 additional subjects who discontinued due to AE had multiple AEs with an action taken as “drug withdrawn,” including ISR AEs and non-ISR AEs.

5.4.1. Common (≥5%) Adverse Events

Across Phase III studies, a higher proportion of subjects who switched to CAB + RPV from SOC reported at least 1 AE. One notable difference observed with the injectable LA formulations compared with the oral formulations of CAB and RPV was the occurrence of ISRs, which is associated with the method of administration. ISRs are discussed in Section 5.4.6.1.

Through Week 48 in Studies 201584 and 201585, the most commonly reported non-ISR AEs occurring in ≥5% of subjects in either the CAB + RPV or CAR group were similar (nasopharyngitis [18% vs. 15%] and upper respiratory tract infection [12% vs. 9%]), and reflect common AEs found in many subjects in studies of 1 year duration (m2.7.4 Section 2.1.1.1). Higher rates of AEs were reported for CAB + RPV than for CAR for hemorrhoids, pyrexia, dizziness, fatigue, headache, nausea, and back pain (m2.7.4 Section 2.1.1.1). The majority of events reported had an intensity of Grade 1 or Grade 2. AEs reported through Week 96 in both studies were consistent overall with trends observed at the Week 48 timepoint (m2.7.4 Section 2.1.1.1).

In Study 207966, the proportion of subjects reporting at least 1 AE (Q8W: 91%; Q4W: 92%) and the frequency of individual common AEs (≥5% in either group) was comparable between the 2 treatment groups, with the exception of injection site nodule, reported by a higher proportion of subjects in the Q4W group (Q8W: 10%; Q4W: 17%) (m2.7.4 Section 2.1.1.1). Non-ISR AEs reported in ≥10% of subjects in either treatment group were nasopharyngitis (14% in both groups) and upper respiratory tract infection (Q8W: 10%; Q4W: 14%).

In Phase II studies, ISRs comprised the most commonly reported AEs (m2.7.4 Section 2.1.1.1). In Study 200056 at Week 160, the most commonly reported non-ISR AEs were nasopharyngitis (38%), diarrhea (22%), and headache (22%) across both randomized IM dosing arms, and nasopharyngitis (14%), back pain (11%), and influenza (11%) across both optimized IM dosing arms. In Study LAI116482 at End of Study, the most commonly reported AEs among subjects receiving CAB were upper respiratory tract infection (36%), diarrhea (29%), nausea (26%), and headache (25%).

5.4.1.1. Drug-Related Adverse Events

In the Phase III studies (201584 and 201585), drug-related AEs (as assessed by the reporting investigator) were more commonly reported for subjects in the CAB + RPV group (who switched their regimen at Baseline) compared with subjects who remained on CAR (m2.7.4 Section 2.1.1.4).

Of the reported drug-related AEs across all Phase III/IIIb studies, the greatest proportion comprised ISRs. ISRs are discussed in Section 5.4.6.1. The most common drug-related non-ISR AEs in Studies 201584, 201585, and 207966 were headache, pyrexia, nausea, asthenia, and fatigue (m2.7.4 Section 2.1.1.4). Overall, few drug-related AEs across Phase III/IIIb studies were treatment limiting.

Across Phase III/IIIb studies, the majority of drug-related AEs were Grade 1 or 2. In Studies 201584 and 201585 at the Week 48 analysis, a numerically higher proportion of subjects in the CAB + RPV group were reported as having Grade 3 to 4 non-ISR, drug-related AEs (1% vs <1% for CAR), predominantly attributable to ISRs, acute viral hepatitis, and AEs of laboratory abnormalities (lipase increase; CPK and AST increase) (m2.7.4 Section 2.1.1). No new Grade 3 or 4 non-ISR drug-related AEs were reported at the Week 96 analysis. In Study 207966, the frequency of Grade 3 or 4 AEs was similar between the Q8W and Q4W groups (3% vs. 5%, respectively). No Grade 5 drug-related AEs occurred in the Phase III studies.

In the Phase II studies, ISRs were the most commonly reported drug-related AEs (m2.7.4 Section 2.1.1.4). In Study 200056 at Week 160, the most commonly reported non-ISR drug-related (per investigator) AEs included pyrexia, headache, fatigue, and influenza-like illness across both IM dosing arms. The most commonly reported drug-related (per investigator) non-ISR AEs in the optimized IM dosing arms included asthenia, fatigue, musculoskeletal stiffness and palpitations, each occurring as isolated events only. In Study LAI116482 through the end of study, non-ISR drug-related AEs reported by ≥10% of subjects were nausea (17%), headache (15%), and diarrhea (10%).

5.4.2. Deaths

A total of 10 deaths (9 in the Safety Population) have been reported in Studies 201584, 201585, 207966, LAI116482, and 200056 (m2.7.4 Section 2.1.2). All cases were considered by the investigators to be unrelated to study drug with the exception of a case of fatal myocardial infarction (Study 200056) where the investigator could not rule out the possibility of relationship to study drug. No deaths were reported in Studies 201584 and 201585 between the Week 48 and Week 96 analyses.

The following deaths were reported during the Phase III studies:

- 1 subject in Study 201584, a 30 to 40-year-old male in the CAR group, died due to a reported homicide during the Induction Phase. The event was reported as a "[redacted]" and not considered related to study treatment.
- 1 subject in Study 201585, a 40 to 50-year old female in the CAR group, died due to a methamphetamine overdose during the Maintenance Phase. This event was not considered related to study drug by the investigator.
- 1 subject in Study 207966, a 40- to 50-year-old male who was randomized to the Q8W group, had previously participated in Study 201585 and had received CAB + RPV LA for 17 months prior to the SAE. The subject presented with an SAE of severe acute pancreatitis 2 weeks after the Week 16 visit in Study 207966. The subject was hospitalized and subsequently experienced cardiopulmonary arrest 2 days after admission. The subject required a prolonged hospital admission over 14 weeks during which over 2 weeks were spent in the ICU. During this time period, the subject experienced multiple serious complications that were also reported as SAEs and culminated in death from sepsis. Death occurred 98 days after the last dose of study medication. The subject had a history of post-endoscopic retrograde cholangiopancreatography pancreatitis, gallstones, and biliary sludge 13 years prior.

This subject also had a history of hyperlipidemia that was being treated with rosuvastatin, which is rarely associated with pancreatitis as an ADR. The investigator considered the pancreatitis possibly related to study drugs as it was not possible to exclude a causative association. Based upon the long latency period and these possible confounders, the Sponsor does not believe the evidence supports the study medication being causative in this instance.

- 1 subject in Study 207966, a 30- to 40-year-old male, was screened de novo for Study 207966 but did not receive a dose of study drug and therefore was not included in the Safety Population. The cause of death was a hemorrhage from a cerebral aneurysm.

The following deaths were reported during the Phase II studies:

- 1 subject in Phase II Study 200056, a 30 to 40-year-old subject in the oral CAB group, died due to a road traffic accident that occurred during the Induction Phase of the study. The event was not considered related to study treatment.
- 1 subject in Phase II Study 200056, a 40 to 50-year-old male in the CAB + RPV group, died due to myocardial infarction after approximately 3 years of CAB + RPV exposure. The subject was a non-smoker with no history of drug use. The subject had cardiovascular risk factors of a BMI of 40 kg/m^2 and adipositas (obesity) and hypertension. An autopsy was performed but the results have not been made available to the study. In spite of potential confounders, the investigator could not exclude that this may have been caused by study drug.
- 1 subject in Phase II Study 200056, a 30 to 40-year-old male in the CAB + RPV group, died due to acute onset refractory epilepsy. The event occurred 48 weeks following initial CAB administration and 32 weeks following initial RPV administration. The subject developed acute onset status epilepticus lasting for approximately 6 hours while alone in his apartment, leading to anoxic brain injury and death. The cause of death was brain death following cerebral edema secondary to refractory epilepsy. An autopsy was not conducted at the family's request. Social history and papaverine detected on urine spectroscopy suggest recreational drug use. The subject had no known prior history of seizure disorder. The event was not considered related to study treatment.
- 1 subject in Phase II Study 200056, a 50- to 60-year-old female, died due to toxicity to various agents (cocaine). The subject had been in the study for over 4 years and was receiving Q4W CAB + RPV at the time of death. The subject had a medical history of diabetes and mild dyslipidemia (elevated total and LDL cholesterol, normal triglycerides). The subject was found dead at home in bed. An autopsy was performed, and the cause of death was reported as cocaine toxicity with atherosclerotic heart disease as a contributory cause. The manner of death was classified as accidental and was not considered related to study treatment.
- 1 subject in Phase II Study LAI116482, a 50 to 60-year old male in the CAB + RPV group, died due gastrointestinal hemorrhage. The event was not considered related to study treatment.

- 1 subject in Phase II Study LAI116482, a 40 to 50-year old male in the CAB + RPV group, died after a cardiac arrest while undergoing elective shoulder repair. The event was not considered related to study treatment.

5.4.3. Other Serious Adverse Events

For Studies 201584 and 201585 (Week 48 analysis), the proportions of subjects developing at least 1 SAE were low and similar between treatment groups in the Maintenance Phase (CAB + RPV 5%; CAR 4%) (m2.7.4 Section 2.1.3.1). The most frequently reported SAEs were Hepatitis A (reported in 4 subjects in the CAB + RPV group and 2 subjects in the CAR group), colitis (reported in 1 subject in the CAB + RPV group and 2 subjects in the CAR group), anal abscess (reported in 0 subjects in the CAB + RPV Q4W group and 2 subjects in the CAR group), and anogenital warts (reported in 1 subject in the CAB + RPV group and 2 subjects in the CAR group). All other SAEs were reported in ≤1 subject each.

At Week 96 in both studies (201584 and 201585), the frequency of SAEs was similar to that observed during the Maintenance Phase for each study (m2.7.4 Section 2.1.3.2). None of the SAEs reported between Week 48 and Week 96 in either study was fatal or drug-related. No patterns of clinical concern for SAEs were noted as individual SAEs were reported across diverse SOCs and PTs for both treatment groups in each study.

In Study 207966, the frequency of subjects reporting at least 1 SAE was similar in the 2 treatment groups (Q8W: 5%; Q4W: 4%) (m2.7.4 Section 2.1.3.1). Three SAEs were reported in more than 1 subject in either treatment group: pneumonia (Q8W: 2 subjects; Q4W: 2 subjects), appendicitis (Q8W: 2 subjects; Q4W: 0 subjects), and hemorrhoids (Q8W: 2 subjects; Q4W: 0 subjects). Otherwise, all SAEs were reported for single subjects in 1 or both treatment groups (ie, ≤2 subjects overall). Two subjects had SAEs related to postinjection reactions after RPV administration (see Section 5.4.8).

In the Phase II studies, no trends of concern were observed (m2.7.4 Section 2.1.3.3). In Study 200056 through 160 weeks of treatment, 38 (17%) CAB + RPV subjects reported a SAE. In Study LAI116482 through End of Study, 36 (20%) CAB + RPV subjects reported a SAE. The majority of SAEs in both studies were single occurrences with no demonstrated trends per study arm.

5.4.4. Drug-Related Serious Adverse Events

In the pooled analysis of Studies 201584 and 201585 (Week 48), 1 subject in each treatment group had a drug-related SAE during the Maintenance Phase (m2.7.4 Section 2.1.4.1). In Study 201584, a subject in the CAB + RPV group had a drug-related SAE of right knee monoarthritis. In Study 201585, a subject in the CAR group had a drug-related SAE of suicidal ideation, and the subject was withdrawn from the study. Between Week 48 and Week 96, no drug-related SAEs were reported in either study.

In Study 207966, SAEs were considered study drug related by the investigator in 3 subjects in the Q8W group and in 1 subject in the Q4W group.

- Injection site abscess (Q8W), see Section 5.4.6.1.
- Presyncope (Q8W), suspected partial IV administration of RPV; see Section 5.4.8.
- Acute pancreatitis (Q8W); this subject died due to sepsis, see Section 5.4.2.
- Hypersensitivity (Q4W), suspected partial IV administration of RPV; see Section 5.4.8.

In Phase II studies, there were few drug-related SAEs (m2.7.4 Section 2.1.4.3). In Study 200056, 1 fatal SAE of myocardial infarction was reported; the investigator could not rule out relatedness to study drug (see Section 5.4.2). In Study LAI116482, 3 drug-related SAEs were reported in 2 subjects in the CAB + RPV group: suicidal ideation and depression (CAB 30 mg; both in same subject) and seizure (CAB 60 mg).

5.4.5. Other Significant Adverse Events

5.4.5.1. Adverse Events Leading to Withdrawal

In Studies 201584 and 201585 (Week 48 analysis), 22 (4%) subjects in the CAB + RPV group and 9 (2%) subjects in the CAR group experienced AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase (m2.7.4 Section 2.1.5.1). Additionally, 1 subject in the CAB + RPV group (Study 201585) had acute hepatitis C and was discontinued due to meeting the protocol-defined liver stopping criteria, which was not captured as an AE leading to withdrawal prior to the data cut-off date. With the exception of acute viral hepatitis (1.7%, 10/591), all non-ISR AEs leading to withdrawal had an incidence of <1%. For ISRs leading to withdrawal, see Section 5.4.6.1.

Table 16 Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Drug During the Maintenance Phase in Study 201584 and Study 201585 (Safety Population)

	201584		201585		POOLED (201584 + 201585)	
System Organ Class Preferred Term	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
Number of Subjects with any event, n (%)	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)
General disorders and administration site conditions						
Asthenia	0	0	1 (<1)	0	1 (<1)	0
Discomfort	1 (<1)	0	0	0	1 (<1)	0
Fatigue	0	1 (<1)	0	0	0	1 (<1)
Infections and infestations[a]						
Hepatitis A	2 (<1)	0	2 (<1)	0	4 (<1)	0
Acute hepatitis B	2 (<1)	0	1 (<1)	0	3 (<1)	0
Acute hepatitis C	1 (<1)	0	0	0	1 (<1)	0
Secondary syphilis	1 (<1)	0	0	0	1 (<1)	0
Nervous system disorders						
Headache	0	0	2 (<1)	0	2 (<1)	0
Amnesia	0	1 (<1)	0	0	0	1 (<1)
Disturbance in attention	0	1 (<1)	0	0	0	1 (<1)
Dizziness	0	1 (<1)	0	0	0	1 (<1)

	201584		201585		POOLED (201584 + 201585)	
System Organ Class Preferred Term	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
Dysarthria	0	1 (<1)	0	0	0	1 (<1)
Memory impairment	0	0	1 (<1)	0	1 (<1)	0
Gastrointestinal disorders						
Diarrhea	1 (<1)	0	1 (<1)	0	2 (<1)	0
Nausea	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Colitis	0	0	0	1 (<1)	0	1 (<1)
Vomiting	1 (<1)	0	0	0	1 (<1)	0
Psychiatric disorders						
Anxiety	0	0	1 (<1)	0	1 (<1)	0
Anxiety disorder	0	0	0	1 (<1)	0	1 (<1)
Depression	0	0	0	1 (<1)	0	1 (<1)
Depression suicidal	0	0	1 (<1)	0	1 (<1)	0
Suicidal ideation	0	0	0	1 (<1)	0	1 (<1)
Suicide attempt	0	1 (<1)	0	0	0	1 (<1)
Investigations						
Blood creatinine increased	0	0	0	1 (<1)	0	1 (<1)
Liver function test abnormal	0	0	1 (<1)	0	1 (<1)	0
Transaminases increased	1 (<1)	0	0	0	1 (<1)	0
Renal and urinary disorders						
Renal failure	0	1 (<1)	0	0	0	1 (<1)
Renal impairment	0	0	0	1 (<1)	0	1 (<1)
Hepatobiliary disorders						
Hepatocellular injury	0	0	1 (<1)	0	1 (<1)	0
Hyperbilirubinemia	0	0	1 (<1)	0	1 (<1)	0
Injury, poisoning and procedural complications						
Overdose	0	0	0	1 (<1)	0	1 (<1)
Musculoskeletal and connective tissue disorders						
Myalgia	0	0	1 (<1)	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Adenocarcinoma of colon	1 (<1)	0	0	0	1 (<1)	0

Data Source: m2.7.4 In-text Table 34.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

a. For details of subjects who withdrew due to acute viral hepatitis, see Table 18.

Between Week 48 and Week 96 in both studies (201584 and 201585), AEs leading to withdrawal were consistent with those observed during the Maintenance Phase (m2.7.4 Section 2.1.5.1). In Study 201584, 5 subjects in the CAB + RPV group withdrew since the Week 48 analysis; 3 of these subjects withdrew during the OLI and never received IM CAB + RPV injections. The other 2 subjects had a total of 4 AEs that led to discontinuation: Hepatitis A, Hepatitis C, injection site pain, and depression. The AEs of injection site pain and depression were assessed as study drug-related; these cases are described in Study 201584 Week 96 CSR [GSK Document Number. 2019N421511_00]. In Study 201585, during the Extension Phase, 2 subjects in the CAB + RPV group had AEs leading to withdrawal of study drug (AEs of Hepatitis B [serious, Grade 3, not related to study treatment] and fear [nonserious, Grade 1, related to study treatment])

[GSK Document Number. 2019N399072_00]. In the Extension Switch to CAB + RPV group, 1 subject had an AE (injection site pain) that led to withdrawal from study drug.

In Study 207966, a total of 12 (2%) subjects in the Q8W group and 13 (2%) subjects in the Q4W group had AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase (m2.7.4 Section 2.1.5.1). Except for fatigue, abnormal dreams, and hyperhidrosis, all in the Q4W group, no individual non-ISR AE term resulted in withdrawal/permanent discontinuation of study drug in >1 subject per treatment group. Ten subjects had non-ISR, Grade 3 or 4 AEs that led to withdrawal of study drug, and 13 subjects had non-ISR, study drug-related AEs that led to withdrawal. ISR AEs leading to withdrawal are detailed in Section 5.4.6.1. The 6 subjects that had Grade 3 or 4, study drug-related AEs that led to withdrawal are listed below:

- Pyrexia (Q8W) – see case narrative in Study 207966 Week 48 CSR [GSK Document Number. 2019N406358_01].
- Presyncope (Q8W) – likely post-injection reaction; see mini narrative in Section 5.4.8.
- Acute pancreatitis (Q8W) – see mini narrative in Section 5.4.2.
- Hypersensitivity (Q4W) - likely post-injection reaction; see mini narrative in Section 5.4.8.
- Transaminases increased (Q4W) – see case narrative in Study 207966 Week 48 CSR [GSK Document Number. 2019N406358_01].
- Depression and fatigue (Q4W) – Subject has a medical history of depression. AEs were reported during OLI and led to withdrawal. See case narrative in Study 207966 Week 48 CSR [GSK Document Number 2019N406358_01].

In Phase II studies, the frequency of AEs leading to withdrawal was consistent with those observed in the Phase III/IIIb studies. In Study 200056 through Week 160, 15 (7%) subjects experienced AEs leading to withdrawal/permanent discontinuation of study drug (m2.7.4 Section 2.1.5.1). In LAI116482 through the end of the study, 12 (7%) subjects in the CAB + RPV group and 9 (15%) subject in the EFV group experienced AEs leading to withdrawal/permanent discontinuation of study drug. For both studies, all AEs leading to withdrawal had an incidence of <1%.

5.4.6. Adverse Events of Special Interest for CAB

AEs of special interest have been identified for CAB (oral and LA) during the CAB + RPV clinical development program based on their relevance in the target population, non-clinical and/or clinical safety data for CAB and RPV (oral and LA), labeling and/or regulatory authority interest, or known association for approved INIs, and/or regulatory authority requirements. Further details about AEs of special interest, as well as supportive data from Phase II studies, are provided in m2.7.4 Section 2.1.6.

There were no expected or observed additive or synergistic effects on AEs of special interest in subjects taking CAB + RPV beyond those effects associated with the individual components.

5.4.6.1. Local Injection Site Reactions

ISRs were only recorded from study drug (CAB + RPV) injections and are expected with IM injections. A detailed analysis of all subject-level and event-level ISR data is presented in m2.7.4 Section 2.1.6.1.

In the pooled Phase III Studies 201584 and 201585, ISRs were very commonly reported (84% of subjects in the CAB + RPV group) (m2.7.4 Section 2.1.6.1). Most subjects had ISRs related to pain (77%), and fewer subjects experienced AEs of nodule (14%), induration (12%), swelling (8%), erythema (4%), and pruritus (4%). Other ISRs occurred less commonly (affecting ≤3% of subjects). Incidence and severity of ISRs decreased over the course of the studies, with approximately 70% of subjects reporting an ISR at first injection to approximately 16% of subjects reporting an ISR at Week 48. Most subjects had ISRs that were Grade 1 (75%) or Grade 2 (36%) in severity and few subjects (1%) discontinued treatment as a result of an ISR. The low rate of discontinuation indicates that while ISRs occurred commonly, they were generally tolerable and resolved in most subjects (88%) within 7 days, with a median duration overall of 3 days. No ISRs in either Study 201584 or Study 201585 were serious.

A post-hoc assessment of treatment acceptance and tolerability (using the PIN instrument) demonstrated consistent results across Studies 201584 and 201585 (m2.7.4 Section 2.1.6.1). The median acceptance of ISRs domain score of the PIN at Week 5 was 2.0 on a 5-point (1=totally acceptable" and 5="not at all acceptable") scale with 2 indicating that the injections were "very acceptable." At Week 48 the median score improved to 1.5, indicating that the injections were between "totally" and "very acceptable." The change in overall acceptance of ISRs from Week 5 to Week 48 was statistically significant; $p < 0.001$; missing data were imputed using LOCF.

At Week 96, the ISRs reported in Studies 201584 and 201585 were consistent with those observed during the Maintenance Phase (m2.7.4 Section 2.1.6.1). In both studies, no ISRs reported as SAEs occurred between the Week 48 LSLV and Week 96 LSLV. In Study 201584, at the end of Maintenance Phase, a total of 3 subjects had ISR AEs leading to withdrawal: 2 subjects had Grade 3 AEs of injection site pain that led to discontinuation of study drug, and 1 subject withdrew consent from the study due to intolerability of injections. In Study 201585 during the Extension Phase, only 1 subject (Extension Switch Population) had 2 AEs of injection site pain that led to withdrawal from study drug. Frequency of ISRs continued to decrease after Week 48 in both studies, mostly due to a reduction in reports of injection site pain.

In Study 207966, overall ISR profiles were similar between treatment groups. The most commonly reported ISR (≥5% of subjects in either treatment group) was injection site pain (Q8W: 371 [72%] subjects; Q4W 363 [70%] subjects) (m2.7.4 Section 2.1.6.1). Other common ISRs were injection site nodules (Q8W: 10%; Q4W: 17%), induration (Q8W: 8%; Q4W: 7%), discomfort (Q8W: 7%; Q4W: 8%), swelling (Q8W: 6%; Q4W: 5%), and pruritus (5% both groups). Relative risk of common ISRs (≥5% of subjects in either treatment group) was similar between treatment groups with the exception of nodules at the injection site, which were reported less frequently in the Q8W group

(m2.7.4 Figure 8). One ISR SAE was reported in the Q8W group (Grade 3 right gluteal abscess) (see mini narrative in m2.7.4 Section 2.1.6.1).

The 2 treatment groups were similar with regards to severity and duration of local ISRs (m2.7.4 Section 2.1.6.1). Most ISRs were Grade 1 or Grade 2, and 3% of subjects in the Q8W group and 4% of subjects in the Q4W group had Grade 3 ISRs. There were no Grade 4 or 5 ISRs. For both groups, the majority of ISRs (86% in both groups) resolved within 7 days and the median duration was 3 days. ISRs lasting more than 14 days occurred in 10% of subjects in the Q8W group and 15% of subjects in the Q4W group.

Five (<1%) subjects in each treatment group had ISRs that led to withdrawal/permanent discontinuation of study drug (m2.7.4 Section 2.1.6.1). Additionally, 1 subject in the Q8W group and 6 subjects in the Q4W group withdrew consent from the study in the absence of AEs, but subjects' stated reasons were injection intolerability, which includes 5 reports of intolerability of injections, 1 report of injection site reactions, and 1 report of pain at site of injection. Overall, 1% of subjects in the Q8W group and 2% of subjects in the Q4W group withdrew from the study due to intolerability of the injections.

High acceptance of ISRs (that include pain and local reactions) following the first injection was reported for both treatment groups at Week 8 (Week 8 measures the acceptance of ISRs during the period following first injection at Week 4) (m2.7.4 Section 2.1.6.1). Acceptance of ISRs significantly improved from first injection through Weeks 24 and 48 for both treatment groups, with similar scores and no significant differences between Q4W and Q8W at any timepoint. These results are supportive of the observation that acceptability of injections improves over duration of treatment irrespective of differences in injection volumes such as between initiation dose and continuation doses (injection volume decreases compared with initiation dose in the Q4W group but remains constant for the Q8W group) and are also consistent with reduction in reporting incidence of ISRs that notably reduces over time through Week 48 for both groups. Numerical improvements were also observed for dimensions Leg Movement and Sleep from Week 8 to Week 24 and 48 for both treatment groups, with a small but significant difference in favor of the Q4W group compared with the Q8W group. No differences were observed for Bother of ISRs dimension and individual items over time or between groups across all timepoints.

5.4.6.2. Hepatotoxicity

The hepatic safety data for CAB supports administration in HIV-infected patients. There have been no events associated with CAB LA that have been assessed as DILI in the clinical program to date.

Phase III Studies

In Study 201584 and Study 201585 (Week 48), 15 subjects met protocol-defined liver monitoring/stopping criteria (m2.7.4 Section 2.1.6.2). Cases for subjects on CAB + RPV were reviewed by an independent hepatic adjudication committee operating under an Adjudication Committee Charter and were assessed to not be attributable to DILI. Of the subjects who met LSC, 11 subjects were in the CAB + RPV group and 3 subjects were in

the CAR group. One subject with liver monitoring criteria in the CAB + RPV group never reached LSC. All of the subjects who met LSC had acute viral hepatitis, and there were more subjects in the CAB + RPV group than in the CAR group who had acute viral hepatitis.

Between Week 48 and Week 96, few additional liver stopping events were reported (m2.7.4 Section 2.1.6.2). In Study 201584, 2 additional subjects (hepatitis A and hepatitis C) in the CAB + RPV group and 1 additional subject (transaminitis) in the CAR group met liver stopping criteria. In Study 201585, 2 additional subjects (acute hepatitis E and acute hepatitis B) in the CAB + RPV group met LSC.

In Study 207966, results were similar to those observed in Studies 201584 and 201585, and there were no clinically relevant differences between the Q8W and Q4W groups (m2.7.4 Section 2.1.6.2). Overall, 5 subjects (2 on Q8W and 3 on Q4W) met LSC during the Maintenance Phase of Study 207966, and 3 additional subjects warranted monitoring based on liver chemistries. Six of these 8 subjects had acute viral hepatitis. Of the 2 subjects who did not, 1 subject had possible DILI that was considered to be related to oral CAB + RPV that was identified during OLI, and 1 subject had liver biochemistry elevations that resolved after discontinuation of a concomitant medication (Melanotan II), which was presumed the likely cause of the elevations. Three of the 8 subjects restarted study drug, and liver biochemistry elevations resolved for 7 of the 8 subjects; the 8th subject's liver biochemistry elevations normalized by Week 56.

Phase I/ II Studies

In the Phase II studies (Study 200056 and Study LAI116482), 18 subjects met LSC (m2.7.4 Section 2.1.6.2). 4 cases of DILI were identified during the Phase II studies (2 cases occurred with subjects receiving CAB 30 mg and 2 cases occurred with subjects receiving CAB 60 mg). All subjects were receiving oral CAB.

During Phase I, 1 additional case of DILI (with CAB 30 mg in a drug interaction study with RBT, Study 205712) was identified and adjudicated by the hepatic adjudication committee.

Of subjects meeting LSC across the CAB + RPV development program, a total of 5 subjects receiving oral CAB have met LSC for which no alternative etiology has been identified and are thus considered to have developed possible or probable DILI or hepatoxicity (m2.7.4 Section 2.1.6.2). Although mild to moderate hepatotoxicity has been identified in these subjects, severe hepatotoxicity [Aithal, 2011] with significant liver dysfunction or liver failure has not been observed. One case of moderate DILI occurred in a subject with chronic active HCV and Grade 3 or Grade 4 fibrosis. The degree of ALT elevation in subjects with DILI was either Grade 3 or Grade 4 in severity. Aminotransaminase elevations in these subjects have been transient and reversible with withdrawal of oral CAB.

Liver chemistry results are discussed in Section 5.5.1.1.

Hepatotoxicity has been observed with INSTIs. Hepatotoxicity has been observed with oral CAB treatment.

5.4.6.3. Hypersensitivity Reactions

Hypersensitivity reactions have been reported as uncommon occurrences with other INSTIs than CAB, characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Delayed type hypersensitivity reactions which have been associated with INSTIs have not been reported with use of CAB to date.

No cases of HSR have been observed following exposure to CAB during the CAB + RPV development program. No subjects were excluded from treatment with CAB LA and RPV LA because of suspected HSR during the OLI.

HSRs are described under Warnings and Precautions in labelling for CAB LA.

Cases of HSR during treatment with CAB LA should be managed with supportive treatment as CAB exposure will continue despite stopping treatment. Use of OLI is recommended to evaluate individual patient tolerability.

During the Maintenance Phase of Studies 201584 and 201585 to Week 48, 13 subjects had AEs that were potentially associated with delayed-type hypersensitivity response (m2.7.4 Section 2.1.6.3). The following AEs were considered to be related to study drug: lip swelling (1 subject in the CAB + RPV group); eosinophilia (1 subject in the CAB + RPV group; 2 subjects in the CAR group). All AEs were Grade 1 or 2 in severity; no Grade 3 or 4 AEs were reported. No SAEs of HSR were reported. None of the events resulted in withdrawal of study treatment or withdrawal from the study.

Through Week 96, there were no additional AE reports suggestive of hypersensitivity in Study 201584 (m2.7.4 Section 2.1.6.3). In Study 201585 to Week 96, 2 AEs suggestive of possible hypersensitivity reactions were reported during the Extension Phase, in subjects in the CAB + RPV arm (m2.7.4 Section 2.1.6.3). Both AEs were Grade 1. Neither event was considered serious, related to study drug, or led to withdrawal from the study.

In Study 207966 through Week 48, 5 subjects in the Q8W group and 6 subjects in the Q4W group had at least 1 AE potentially associated with HSR (m2.7.4 Section 2.1.6.3). All AEs were Grade 1 or 2 with the exception of 1 Grade 3 SAE reported as hypersensitivity (Q4W group). The SAE was considered to be related to study drug and was associated with partial IV injection of RPV. The SAE led to withdrawal from the study drug. See Section 5.4.8 for details; a full case narrative is provided in GSK Document Number 2019N406358_01, Section 13. One other AE of potential HSR was also considered to be related to study drug (Q8W group). This subject had a non-serious, Grade 2 AE of injection site hypersensitivity. Other AEs with the same onset in this subject were injection site discoloration, injection site swelling, injection site warmth, and high fever after injection. The AE of injection site hypersensitivity led to withdrawal from study drug. All other AEs of potential HSR were considered not related to study drug.

5.4.6.4. Rash

During Phase III Studies 201584 and 201585 (through Week 96) and Phase IIIb Study 207966 (through Week 48), there were no reports involving severe rash or events such as Stevens-Johnson Syndrome, Erythema multiforme or Toxic Epidermal Necrolysis. Grade 1 and Grade 2 rashes were reported with treatment with CAB + RPV (m2.7.4 Section 2.1.6.4). Serious AEs or Grade 3 or Grade 4 rashes have not been reported with CAB + RPV. Most events did not lead to withdrawal. In Studies 201584 and 201585, the incidence of rash in the CAB + RPV groups was comparable to CAR.

Rash is considered an ADR for treatment with CAB + RPV.

5.4.6.5. QT Prolongation

CAB has not been observed to have an effect on QT prolongation. Treatment with CAB + RPV does not have clinically relevant effects on the QT interval.

In Study 201584 and Study 201585 through Week 48, treatment with CAB and RPV did not have any clinically relevant effect on the corrected QT interval of the ECG (m2.7.4 Section 2.1.6.5). No AEs of QT prolongation were reported between Week 48 and Week 96 in either study.

In Study 207966 through Week 48, ECG results were similar between treatment groups (m2.7.4 Section 2.1.6.5). Overall, treatment with CAB and RPV did not have any clinically relevant effect on the corrected QT interval of the ECG.

Oral CAB was evaluated in a thorough QT study (Study LAI117009). The study demonstrated that CAB had no impact on prolongation of the QT interval (m2.7.4 Section 2.1.6.5).

5.4.6.6. Neuropsychiatric Adverse Events

Mood and sleep disorders are common in the HIV infected population. These include irritability, insomnia, abnormal dreams. Integrase inhibitors are associated with reports of mood disorders (anxiety and depression), suicidal ideation and sleep disorders (abnormal dreams and insomnia). Therefore, depression and suicidal ideation are events of special interest in the CAB + RPV development program.

Neuropsychiatric AESIs occurring in >1% of subjects in all treatment groups in Studies 201584, 201585, and 207966 were those potentially related to depression, anxiety, or sleep disorders (Table 17). All other neuropsychiatric AESIs occurred in ≤1% of subjects in all treatment groups. AEs of bipolar disorder and psychosis were infrequently reported during the Phase III/IIIb studies.

Table 17 Summary of Neuropsychiatric AESIs in Studies 201584, 201585, and 207966 - Maintenance Phase (Safety Population)

Neuropsychiatric AESI	Pooled Studies 201584 and 201585 (Week 48)		Study 207966 (Week 48)	
	CAB + RPV Q4W N=591 N (%)	CAR N=591 N (%)	CAB + RPV Q8W N=522 N (%)	CAB + RPV Q4W N=523 N (%)
Suicidal Ideation and Behavior	4 (<1)	5 (<1)	1 (<1)	0
Depression	16 (3)	14 (2)	12 (2)	14 (3)
Anxiety	27 (5)	20 (3)	22 (4)	14 (3)
Mood Disorders	7 (1)	1 (<1)	4 (<1)	2 (<1)
Bipolar Disorder	0	0	1 (<1)	0
Psychosis	1 (<1)	0	1 (<1)	0
Sleep Disorders	38 (6)	21 (4)	22 (4)	36 (7)

Data Sources: m2.7.4 Table 50.

In Phase III Studies 201584 and 201585 and Phase IIIb Study 207966 (through Week 48), subjects with a past history of psychiatric illness and specifically in the categories of depression, anxiety, and suicidal ideation had a higher incidence of these events reported during the studies (m2.7.4 Section 2.1.6.6).

Suicidal Ideation and Behavior

Suicidality assessments were collected prospectively during Phase III/IIIb studies using the eC-SSRS (m2.7.4 Section 2.1.6.6). A summary of cases of validated possible suicidality related AEs is provided in m2.7.4 Section 4.4. Serious events potentially related to suicidal ideation or behavior were reported at low incidence with treatment with CAB + RPV.

There were no completed suicides in Study 201584 and Study 201585 (m2.7.4 Section 2.1.6.6). In the pooled analysis, validated true positive alerts for suicidality assessments occurred at a lower incidence in the CAB + RPV group compared with the CAR group (3 subjects [<1%] in the CAB + RPV group; 6 subjects [1%] in the CAR group).

In both studies, the overall incidence of suicidal ideation and behavior in the CAB + RPV group was comparable to CAR (4 [<1%] subjects in the CAB + RPV group and 5 [<1%] subjects in the CAR group had AEs of suicidal ideation or behavior) (m2.7.4 Section 2.1.6.6). The onset appeared to be early in treatment during Study 201584 and Study 201585.

There were no serious events of suicidal ideation and suicidal attempts in Study 201584 and Study 201585 in subjects receiving CAB + RPV at Week 48. In Study 201584, 2 subjects in the CAR group had neuropsychiatric SAEs (drug abuse 1 subject, suicide attempt 1 subject). The SAE of suicide attempt in the CAR group was not considered related to study drug but did result in withdrawal of the subject from the study.

In most cases, treatment with CAB + RPV was continued without interruption. One subject in Study 201585 in the CAB + RPV group was withdrawn from the study due to an AE of depression suicidal.

In Study 201584 and Study 201585 between Week 48 and Week 96 analyses, there were no AEs reported that were potentially related to suicidal ideation or behavior in either the Safety or Extension Switch Populations (m2.7.4 Section 2.1.6.6).

No completed suicides occurred in Study 207966 through Week 48 (m2.7.4 Section 2.1.6.6). No AEs of suicide or suicide attempts were reported. 12 (2%) subjects in the Q8W group and 21 (4%) subjects in the Q4W group reported suicidal ideation or behavior during the Maintenance Phase. Possible suicidality-related AEs (PSRAE) data showed 5 (<1%) subjects in each treatment group with suicidal ideation or behavior alerts. Of these, 2 subjects (1 Q8W; 1 Q4W) had positive PSRAEs.

Incidence of suicidal ideation and behavior was low (<1%) across the Phase III/IIIb studies. Suicidal ideation and behavior is not considered attributable to treatment with CAB + RPV.

Depression

Incidence of depression was low (≤3%) in subjects treated with CAB + RPV across the Phase III/IIIb studies. Depression is an ADR for treatment with CAB + RPV.

In the pooled Phase III Studies 201584 and 201585 (through Week 48), 16 (3%) subjects in the CAB + RPV group had AEs of depression (m2.7.4 Section 2.1.6.6). The incidence was comparable to CAR (14 subjects [2%]). There were no serious AEs of depression with CAB + RPV. Most events did not lead to withdrawal.

At Week 96 in Study 201584, Since the Week 48 analysis, there were 2 new AEs of depression (Grade 1 and Grade 2), both considered related to study drug, which resulted in withdrawal from the study. At Week 96 in Study 201585, there were no new SAEs or AEs leading to withdrawal that were potentially related to depression in either the Safety or Extension Switch Populations.

In Study 207966 through Week 48, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to depression (m2.7.4 Section 2.1.6.6). 1 subject in the Q8W group had an SAE of major depression that was considered not related to study drug and did not lead to withdrawal. The same subject had a concurrent SAE of substance-induced psychotic disorder. 1 subject in the Q4W group had an AE of depression considered related to study drug that led to withdrawal.

Mood Disorders

Mood disorders included affect lability, affective disorder, irritability, mood altered, mood swings, lethargy. Events of mood disorders were reported at a low incidence (≤1%) with treatment with CAB + RPV across the Phase III/IIIb studies.

In Study 201584 and Study 201585 at Week 48, events of mood disorders were reported with treatment with CAB + RPV (m2.7.4 Section 2.1.6.6). The incidence was higher

compared with that of the CAR group (7 [1%] subjects in the CAB + RPV group and 1 [<1%] subjects in the CAR group) during Phase III studies although the incidence of drug-related events was comparable (3 subjects in the CAB + RPV group and 1 subject in the CAR group). There were no serious events of mood disorders with CAB + RPV during Phase II and Phase III studies. Severity was generally Grade 1 or Grade 2. Mood disorder events did not lead to withdrawal. Although there was a higher incidence of mood disorders with CAB + RPV, review of the individual cases did not suggest a compelling association between mood disorders and treatment with CAB + RPV.

At Week 96 in Studies 201584 and 201585, there were no SAEs or AEs leading to withdrawal that were potentially related to mood disorders in either the Safety or Extension Switch Populations (m2.7.4 Section 2.1.6.6).

In Study 207966 through Week 48, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to mood disorders (m2.7.4 Section 2.1.6.6). There were no SAEs or AEs leading to withdrawal potentially related to mood disorders reported in either treatment group.

Mood disorders are not considered attributable to treatment with CAB + RPV.

Sleep Disorders

Events of sleep disorders were reported with treatment with CAB + RPV. The incidence of sleep disorders was ≤7% in any treatment group across the Phase III/IIIb studies. Insomnia and abnormal dreams are ADRs for treatment with CAB + RPV.

In Study 201584 and Study 201585 at Week 48, events of sleep disorders were reported with treatment with CAB + RPV (38 [6%] subjects in the CAB + RPV group and 21 [4%] subjects in the CAR group) (m2.7.4 Section 2.1.6.6). The incidence of events (including drug-related events), particularly insomnia, was higher in the CAB + RPV group compared with CAR during Study 201584 and Study 201585 (22 [4%] subjects in the CAB + RPV group and 8 [1%] subjects in the CAR group). There were no serious events of sleep disorders with CAB + RPV during Phase II and Phase III studies. Severity was generally Grade 1 or Grade 2. Sleep disorder events did not lead to withdrawal. Sleep disorders including abnormal dreams, and insomnia are considered associated with treatment with CAB + RPV.

At Week 96, there were no new SAEs or AEs leading to withdrawal that were potentially related to sleep disorders in either the Safety or Extension Switch Populations in Studies 201584 and 201585 (m2.7.4 Section 2.1.6.6).

In Study 207966 through Week 48, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to sleep disorders. 1 subject had a sleep disorder-related SAE and 2 subjects had sleep disorder-related AEs that led to withdrawal (m2.7.4 Section 2.1.6.6).

- 1 subject in the Q4W group had an SAE (Grade 3 sleep apnea) that was not related to study drug and no change was made to study drug.
- 1 subject in the Q4W group had 2 Grade 2 AEs (abnormal dreams, sleep disorder) simultaneously that were both considered to be related to study drug and led to withdrawal of study drug.

- 1 subject in the Q4W group had 2 Grade 1 AEs (abnormal dreams, insomnia) simultaneously that were considered to be related to study drug and led to withdrawal of study drug.

Anxiety

Anxiety has been reported at a low incidence (≤5% in any treatment group) with CAB + RPV across Phase III/IIIb studies. Anxiety is an ADR for CAB+RPV.

In Study 201584 and Study 201585 at Week 48, the incidence of anxiety-related events with CAB + RPV was comparable with CAR (m2.7.4 Section 2.1.6.6). Study drug-related AEs of anxiety were reported at a higher incidence in the CAB + RPV group than in the CAR group (8 [1%] subjects vs. 1 [<1%] subject, respectively). No SAEs of anxiety were reported. One subject in each treatment group had AEs of anxiety that led to withdrawal.

At Week 96 in Study 201584, no new SAEs of anxiety or AEs of anxiety that led to withdrawal were reported (m2.7.4 Section 2.1.6.6). At Week 96 in Study 201585, there were no SAEs that were potentially related to anxiety in either the Safety or Extension Switch Populations (m2.7.4 Section 2.1.6.6). In the Safety Population, 1 subject had an AE of anxiety that led to withdrawal and 1 subject had an AE of fear that led to withdrawal; both were considered related to study drug.

In Study 207966, through Week 48, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to anxiety. None of the anxiety-related AEs were serious and none led to discontinuation of study drug (m2.7.4 Section 2.1.6.6).

5.4.6.7. Seizures and Seizure-like Events

A small number of seizures have been reported during CAB development which prompted enhanced monitoring of similar events. Based on the clinical, preclinical and secondary pharmacology data available, as well as individual case details, and expected rates of seizures in the overall HIV positive and negative population, there is no convincing evidence that CAB exposure is associated with seizure or with reduction of seizure threshold.

In the Phase III Studies 201584 and 201585 at Week 48 and at Week 96 analyses, there were no SAEs related to seizure and no AEs of seizure that led to withdrawal from study drug (m2.7.4 Section 2.1.6.7). None of the AEs of seizure were study drug related.

In Study 207966, through Week 48, 1 subject in the Q8W group had a Grade 3 SAE of epilepsy (m2.7.4 Section 2.1.6.7). This subject died of sepsis during the study (see Section 5.4.2). 3 subjects in the Q4W group had AEs of syncope, without any additional evidence of seizures, none of which were serious or lead to withdrawal. Additional details regarding potential seizure-related AEs can be found in m2.7.4 Section 2.1.6.7.

5.4.6.8. Weight Gain

Weight gain has been reported with another INSTI, DTG. Weight gain is associated with treatment with CAB + RPV. Additional details about weight gain are presented in Section 5.6.2.

In the Phase III studies (201584 and 201585) at Week 48, a trend towards slight weight gain was observed for subjects in the CAB + RPV group (pooled median change 1.5 kg compared with 1.0 kg for the CAR group) (m2.7.4 Section 2.1.6.8). Most subjects had minor shifts in their BMI, including some who had a decrease in BMI at Week 48, although most shifts were increases. Notably weight gain shifts affected both CAB + RPV and CAR groups. One of the events of weight gain in the CAB + RPV group was considered to be drug-related. No SAEs and no withdrawals due to AEs of weight gain were reported in Studies 201584 and 201585.

Between the Week 48 and Week 96 analyses in Study 201584, 8 subjects in the CAB + RPV group and 3 subjects in the CAR group had an AE of weight gain (m2.7.4 Section 2.1.6.8). At the Week 96 analysis in Study 201585, 1 new AE of weight increase and 2 new AEs of weight decrease were reported (m2.7.4 Section 2.1.6.8). No SAEs and no withdrawals due to AEs of weight gain were reported in either study.

In Study 207966 through Week 48, median weight gain from Baseline was 1.0 kg in both treatment groups. 9 subjects (2%) in the Q8W group and 4 subjects (<1%) in the Q4W group reported at least 1 AE possibly indicative of weight gain (m2.7.4 Section 2.1.6.8). None were SAEs or led to withdrawal from study drug.

5.4.6.9. Rhabdomyolysis

Rhabdomyolysis has been reported with another INSTI, RAL. Myalgia is an ADR for treatment with CAB + RPV. There was no evidence of safety concerns regarding rhabdomyolysis with treatment with CAB + RPV.

Rhabdomyolysis was not observed in Study 201584 through Week 48 (m2.7.4 Section 2.1.6.9). In Study 201585 at Week 48, 1 case in the CAR group was reported; it was Grade 3 in severity, was not serious, was not considered study drug-related, and did not lead to withdrawal.

In the pooled analysis of Studies 201584 and 201585, more subjects in the CAB + RPV group had AEs of myalgia compared with those in the CAR group (24 [4%] subjects compared with 8 [1%] subjects, respectively) (m2.7.4 Section 2.1.6.9). 1 AE of myalgia (CAB + RPV group) led to study drug discontinuation. Grade 3 and Grade 4 elevations of CK were observed in 47 (8%) subjects during Phase III trials for CAB + RPV through 48 weeks of treatment, compared with 26 (4%) subjects in the CAR group (m2.7.4 Section 2.1.6.9). These CK elevations were transient, asymptomatic and generally associated with subjects reporting strenuous exercise and/or weight lifting.

Between Week 48 and Week 96 in Study 201584, 4 additional CAB + RPV Q4W subjects and 2 additional CAR subjects had AEs of myalgia. None of the AEs of myalgia were serious or led to withdrawal; all were Grade 1 or 2 (m2.7.4 Section 2.1.6.9). In

Study 201585, no new AEs of blood creatine phosphokinase increase, myalgia, or rhabdomyolysis were reported.

In Study 207966 through Week 48, 25 subjects (Q8W: 10 subjects; Q4W: 15 subjects) had AEs of myalgia; none of the reports of myalgia were SAEs. One subject in the Q4W group withdrew due to myalgia, assessed as Grade 2 and related to study drug. Myalgia was 1 of 11 AEs leading to withdrawal for this subject. Rhabdomyolysis was reported for 1 subject in the Q8W group; it was Grade 2, not considered drug related, not serious, and did not result in withdrawal of the subject from the study. The subject also had a Grade 4 AE of blood CPK increased. Both the AEs of rhabdomyolysis and blood CPK increased were considered secondary to exercise.

5.4.6.10. Pancreatitis

Pancreatitis has been reported with another INSTI (RAL), and other NNRTIs. There was no evidence of safety concerns regarding pancreatitis with treatment with CAB + RPV.

In Studies 201584 and 201585 through Week 48, 3 (<1%) subjects in the CAB + RPV group (n=4 events) and no subjects in the CAR group had AEs potentially associated with pancreatitis (m2.7.4 Section 2.1.6.10). One of the cases reported in Study 201585 was an SAE of acute pancreatitis; the event was not considered study drug related and it resolved within 5 days. None of the other events were serious, drug-related, or led to study drug discontinuation.

At Week 96 in the Phase III studies, no new cases of pancreatitis were reported in Study 201584, and only 1 potential case of pancreatitis was reported in Study 201585, which was a subject in the Extension Switch to CAB + RPV group (m2.7.4 Section 2.1.6.10). This AE was non-serious, not related to study drug, and did not lead to withdrawal from study drug.

In Study 207966 through Week 48, 2 subjects had reports of pancreatitis AEs (both in Q8W group) (m2.7.4 Section 2.1.6.10). One was Grade 1, non-serious, and no change was made to the study drug. The other event was a Grade 4 SAE that was considered by the investigator to be study drug related, although the Sponsor considered it to be unrelated to study drugs, that resulted in withdrawal of the subject; this subject had additional complications and died due to sepsis (see Section 5.4.2 for details).

5.4.6.11. Impact on Creatinine

Creatinine elevation without evidence of worsening renal function is associated with DTG, a closely related INSTI. There was no evidence that treatment with CAB + RPV led to clinically relevant worsening of renal function.

During Study 201584 and Study 201585 (pooled through Week 48), a non-clinically significant median decrease in serum creatinine from Baseline was observed with treatment with CAB + RPV at Week 48 (m2.7.4 Section 2.1.6.11). This decrease may represent a switch from DTG to CAB, since CAB, in contrast to DTG, does not inhibit

the OCT2 transporter and thus does is not expected to elevate creatinine levels. No clinically significant changes were observed in the CAR group.

Subjects with moderate (Grade 2) renal impairment at Baseline, and treated with CAB + RPV, were not observed to have worsening of renal impairment during 48 weeks of treatment (m2.7.4 Section 2.1.6.11).

Between Week 48 and Week 96, no new cases of blood creatinine increased were reported in either study (m2.7.4 Section 2.1.6.11). In Study 201584, 1 additional subject in the CAB + RPV Q4W group had an AE of renal impairment since the Week 48 analysis; it was not related to study drug. In Study 201585, 2 subjects in the Extension Switch to CAB + RPV group reported AEs (Grade 1; Grade 2) of creatinine renal clearance decreased. Both AEs were considered related to study drug; the study drug dose was not changed nor discontinued.

In Study 207966 through Week 48, 2 subjects (both in the Q8W group) had renal and urinary disorders AEs that potentially indicated an impact of CAB + RPV on creatinine (m2.7.4 Section 2.1.6.11). One subject had an AE of renal impairment that was considered related to study drug but did not lead to withdrawal. Another subject had a Grade 4 SAE of acute kidney injury that was considered not related to study drug; the subject later died due to sepsis (see Section 5.4.2). There were no other AEs related to pancreatitis that were serious and none of the AEs of pancreatitis led to study drug discontinuation.

5.4.6.12. Safety of CAB + RPV in Pregnancy

The safety of CAB + RPV during human pregnancy has not been established (Section 5.8).

For a summary of non-clinical results relating to pregnancy, see m2.4 Section 4.6.

When CAB was administered to pregnant rats (at >30 times the systemic exposure at the maximum recommended human dose [MRHD] of 30 mg) during the period of organogenesis through delivery, there were adverse effects on labor and delivery that may be related to a delay in the onset of parturition and which led to increased fetal mortality (stillbirths) and neonatal deaths immediately after birth. There was no fetal mortality when rat fetuses were delivered by cesarean.

CAB + RPV should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus (m2.7.4 Section 5.4.1).

During the Phase III Studies 201584 and 201585 to Week 48, 8 pregnancies were reported in subjects exposed to CAB (1 oral only and 7 long acting) (Section 5.8). There were 2 AEs associated with pregnancy: 1 subject (CAR group) had an SAE of spontaneous abortion and 1 subject (CAB + RPV) had an SAE of abortion missed (medical termination for anembryonic pregnancy) (m2.7.4 Section 2.1.6.12). The outcomes of the remaining pregnancies in the CAB + RPV group were 2 live births of a healthy infant, 1 ongoing pregnancy at the time of database lock, and 3 subjects electively

terminated the pregnancy for non-medical reasons. In the CAR group, 1 live birth and 1 induced abortion were additionally reported.

Between Week 48 and Week 96, no new pregnancies were reported and no SAEs related to ongoing pregnancies were reported in Studies 201584 and 201585 (m2.7.4 Section 2.1.6.12).

In Study 207966 through Week 48, 4 pregnancies were reported (Section 5.8). One pregnancy in the Q4W group resulted in spontaneous abortion (SAE) considered unrelated to study drug (m2.7.4 Section 2.1.6.12). The outcomes of the remaining pregnancies were elective abortion for non-medical reasons (Q8W, n=1; Q4W, n=1), and ongoing pregnancy at time of data cut-off (Q4W, n=1).

5.4.7. Adverse Events Reported During OLI

An OLI of CAB + RPV was included in the Phase III/IIIb studies to evaluate the potential in each subject for ADRs which would preclude IM dosing. Total exposure numbers in the clinical program can be found in Section 1.2. In Phase III pooled studies 201584 and 201585 through Week 48, 590 subjects received OLI. In Study 207966, 655 subjects received OLI. In Studies LAI116482 and 200056, there was no OLI period.

During the OLI period in Studies 201584 and 201585, 6 (1%) subjects (3 subjects in each study) experienced AEs leading to withdrawal/permanent discontinuation of study drug (m2.7.4 Section 2.1.8). AEs leading to withdrawal in Study 201584 were acute hepatitis C (Grade 2), hepatitis A (Grade 4), and transaminases increased (Grade 3, due to solvent abuse). AEs leading to withdrawal in Study 201585 were asthenia (Grade 2), myalgia (Grade 2), headache (Grade 3), and depression suicidal (Grade 2). There were no reports of HSR or DILI, and no withdrawals due to AEs during that period that could have represented early HSR or DILI. Cases of DILI were observed in prior studies with oral CAB dosing (see Section 5.4.6.2).

In Study 207966 during OLI, 1 subject had a Grade 3 AE of increased transaminases and the case was adjudicated as possible DILI (Section 5.4.6.2), and the subject was withdrawn from the study. No subjects had AEs consistent with hypersensitivity that led to withdrawal.

To date, all studies (with the exception of Study LAI114433) conducted with CAB LA + RPV LA included a period of oral dosing with CAB + RPV (induction/OLI) prior to IM dosing in order to evaluate individual subject tolerability.

5.4.8. Post-injection Reactions

Inadvertent partial IV injections have been identified infrequently during the CAB + RPV clinical development program. Transient high plasma levels could theoretically lead to a risk from transient overexposure to drug and could also lead to a risk of virologic failure, as systemic concentrations would fall more quickly than from an IM injection.

Ad hoc analysis of CAB and RPV plasma concentrations measured 2 hours postdose at several visits during the Phase IIb/III/IIIb Studies 200056, 201584, 201585, and 207966 suggest that inadvertent (partial) IV injections occurred infrequently (~0.8% of the ~4996 2-hour post injection CAB and RPV concentrations measured) and in most cases, without significant AEs or impact on virologic expression (m2.7.4 Section 2.1.7). No specific AEs have been associated with unexpectedly high CAB concentrations.

Across the CAB development program, 4 subjects were reported to have post-injection reactions; 3 were apparently associated with inadvertent intravenous injection of RPV (based on PK) (m2.7.4 Section 2.1.7). The fourth case was not confirmed as due to inadvertent IV administration because a suitably timed post dose PK sample was not collected. The cases were reported in Study 207966 (n=3) and in Study 200056 (n=1). These reactions occurred within minutes of the injection and began to resolve within a few minutes after onset.

As an estimated 40,000 RPV LA injections have been administered in the CAB + RPV development program, these events appear to be very rare. While the mechanism for these events is currently not known, the reported events have been characterized by rapid improvement of associated signs and symptoms. In each case, the treating physicians and study sites had been participating in the CAB + RPV trials for several years and were experienced with administering injections.

5.5. Clinical Laboratory Evaluations

5.5.1. Clinical Chemistry

Results of the clinical laboratory findings demonstrate that there are no laboratory signals of concern in subjects switching from CAR to receiving CAB + RPV treatment (m2.7.4 Section 3.1). In Studies 201584 and 201585 to Week 48, the majority (75% for CAB + RPV, 80% for CAR) of the post-Baseline emergent clinical chemistry toxicities were Grade 1 or Grade 2 in intensity. No clinically relevant differences were observed overall in Grade 3 and Grade 4 post-Baseline emergent toxicities between the CAB + RPV and CAR groups. At Week 96, trends in clinical laboratory parameters were consistent with those observed at Week 48 for both studies. In Study 207966, there were no clinically relevant differences between treatment groups for overall clinical chemistry abnormalities (including liver chemistry) in either frequency or toxicity grade, and no new safety concerns were identified in clinical chemistry parameters.

5.5.1.1. Liver Chemistry Results

A few subjects had transaminase elevations attributed to suspected hepatotoxicity in relation to exposure to CAB in Phase I and Phase II trials (m2.7.4 Section 2.1.6.2). Elevated transaminases (AST/ALT) were observed in subjects receiving CAB + RPV during the pivotal Phase III trials, however, the primary reason for these elevations was the occurrence of acute viral hepatitis (hepatitis A, B, C). A summary of AEs potentially related to hepatotoxicity and liver monitoring and stopping events is presented in Section 5.4.6.2.

Phase III Studies

In the pooled analysis of Study 201584 and Study 201585 to Week 48, 15 subjects met protocol-defined liver monitoring/stopping criteria (Table 18). 1 subject in the CAB + RPV group met liver monitoring criteria, but never reached liver stopping criteria. 11 subjects with liver stopping criteria were in the CAB + RPV group and 3 subjects were in the CAR group.

10 subjects had acute viral hepatitis in the CAB + RPV group (6 subjects in Study 201584 and 4 subjects in Study 201585) (m2.7.4 Section 3.1.1.1). 3 subjects had acute viral hepatitis in the CAR group (2 subjects in Study 201584 and 1 subject in Study 201585). The other 2 cases of LSC were due to transaminitis related to illicit drug use and inorganic solvent abuse and known Gilbert's disease with reported alcohol use prior to the clinic visit.

There were no cases of DILI reported to Week 48 in Study 201584 and Study 201585 (m2.7.4 Section 3.1.1.1). Hepatotoxicity and cases meeting LSC are discussed in Section 5.4.6.2.

Table 18 Subjects with Liver Monitoring/Stopping Events in Phase III Study 201584 and Study 201585 (Week 48 Analysis)

Study	Treatment Group	Study Phase	ALT	AST	Total Bilirubin	Resolved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201584	CAB + RPV	MP – oral (Week 4)	20.8xULN	12.5xULN	WNL	Y	Y	Acute hepatitis C
201584	CAB + RPV	MP – oral (Week 4)	8.8xULN	3.1xULN	1.5xULN	Y	Y	Acute hepatitis A
201584	CAB + RPV	MP – oral (Baseline)	43.7xULN	36.5xULN	1.3xULN	Y	Y	Illicit IV drug use, inorganic solvent abuse, chronic hepatitis C
201584	CAB + RPV	MP – LA (Week 20)	30.2xULN	17.9xULN	1.7xULN	N	Y	Acute hepatitis B
201584	CAB + RPV	MP – LA (Week 32)	98.1xULN	89.3xULN	6.9xULN	Y	N, Restarted Treatment	Acute Hepatitis A
201584	CAB + RPV	MP – LA (Week 24)	7.4xULN	≥6.7xULN	1.7xULN	Y	N	Liver monitoring event. Never met liver stopping criteria. Alcohol use 2 days before

Study	Treatment Group	Study Phase	ALT	AST	Total Bilirubin	Resolved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
								study visit; AE of direct bilirubin increased (known Gilbert's)
201584	CAB + RPV	MP – LA	155xULN	176.5xULN	7xULN	Y	Y	Acute hepatitis A
201584	CAB + RPV	MP – LA (Week 44)	8.1xULN	5.3xULN	1.5xULN	Y	Y	Acute hepatitis B
201584	CAR	MP (Week 36)	10.4xULN	6.0xULN	WNL	Y	Y	Acute Hepatitis E
201584	CAR	MP (F/U 3 weeks after Week 8)	24.1xULN	18.5xULN	5.3xULN	Y	Y	Acute Hepatitis A
201585	CAB + RPV	MP – LA (Week 12)	42.9xULN	29.2xULN	1.2xULN	Y	Y	Acute hepatitis B
201585	CAB + RPV	MP – LA (Week 36 to 40)	14.7xULN	6.7xULN	1.3xULN	Y	Y	Acute Hepatitis A
201585	CAB + RPV	MP – LA (Week 16)	8.6xULN	4.8xULN	8xULN	Y	Y	Acute Hepatitis A
201585	CAB + RPV	MP – LA (Week 24)	21.6xULN	8.4xULN	2.1xULN	N	Y	Acute hepatitis C
201585	CAR	MP (Week 8)	10.4xULN	4.5xULN	5.6xULN	Y	N, Restarted treatment	Acute Hepatitis A

Data Source: m2.7.4 In-text Table 44.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: liver chemistry parameters represent peak values.
Note: Each line represents an individual subject.

Between Week 48 and Week 96 in Study 201584, 2 additional subjects in the CAB + RPV group and 1 additional subject in the CAR (Extension Switch to CAB + RPV) group met LSC (m2.7.4 Section 2.1.6.2). The 2 subjects in the CAB + RPV Q4W group had acute viral infections (hepatitis A and hepatitis C) and were withdrawn from treatment due to meeting LSC. The subject in the CAR group had transaminitis and a concurrent event of acute cholecystitis (an SAE) and resumed treatment following normalization of LFTs and resolution of acute cholecystitis. At Week 96 in Study 201585, 2 additional

subjects in the CAB + RPV group met LSC (m2.7.4 Section 2.1.6.2). One subject had acute hepatitis E and the other subject had acute hepatitis B.

In Study 207966, 5 subjects in the Q8W group and 13 subjects in the Q4W group had ALT ≥3xULN (Table 19). 5 subjects met LSC (2 subjects in the Q8W group, 3 subjects in the Q4W group). 3 additional subjects in the Q4W group were monitored for abnormal liver chemistries but did not meet LSC. Six of these subjects had acute viral hepatitis and 1 subject was taking a nonprescribed medication, Melanotan II (alpha-melanocyte-stimulating hormone analogue). One case of probable DILI was reported in a subject in the Q4W group during OLI. Hepatotoxicity and cases meeting LSC are discussed in Section 5.4.6.2. Further details of liver chemistry results for Study 207966 are provided in m2.7.4 Section 3.1.1.

Table 19 Summary of Subjects with ALT Greater Than or Equal to 3X ULN During the Maintenance Phase in Study 207966 (Safety Population)

Hepatobiliary Criteria[a,b]	Q8W (N=522)	Q4W (N=523)
ALT ≥3 x ULN to <5 x ULN	3 (<1)	8 (2)
ALT ≥5 x ULN to <10 x ULN	1 (<1)	3 (<1)
ALT ≥10 x ULN to <20 x ULN	0	0
ALT≥20 x ULN	1 (<1)	2 (<1)

a. Subjects may be counted in more than one category.
Data Source: GSK Document Number 2019N406358_01 Table 3.57.

Phase II Studies

Elevated aminotransferases have been observed with exposure to oral CAB in the Phase IIb studies during the CAB + RPV development program (m2.7.4 Section 3.1.1.3).

Most subjects who met LSC in Phase II were due to acute viral hepatitis (m2.7.4 Section 2.1.6.2). There were 4 cases of DILI on oral CAB that occurred in Phase II. 1 subject on oral CAB in Phase I Study 205712 also met LSC due to suspected DILI.

5.5.1.2. Creatine Kinase

Reported creatine kinase elevations were considered to be exercise related. AEs potentially related to rhabdomyolysis are presented in Section 5.4.6.9.

Phase III Studies

In Study 201584 and 201585, during the Maintenance Phase to Week 48, 122 subjects in the CAB + RPV group and 94 subjects in the CAR group had post-Baseline-emergent elevated CK levels, with 47 cases observed in the CAB + RPV group with Grade 3 or Grade 4 intensity compared with 26 in the CAR group (m2.7.4 Section 3.1.6). Reported CK elevations were considered to be exercise related.

At Week 96 in Study 201584, there were 11 new Grade 3 or 4 cases of post-Baseline-emergent elevated CK levels (10 in the CAB + RPV group vs. 1 in the CAR [Extension Switch to CAB + RPV] group) (m2.7.4 Section 3.1.6). At Week 96 in Study 201585, there were 4 new Grade 3 or 4 cases of post-Baseline-emergent elevated CK levels (3 in the CAB + RPV group vs. 1 in the Extension Switch to CAB + RPV group).

In Study 207966, there were no clinically relevant differences between treatment groups (79 [15%] subjects in Q8W vs. 74 [14%] subjects in Q4W) and no change from Baseline for CK results (m2.7.4 Section 3.1.6).

Phase II Studies

During the Phase II studies (Study LAI116482 end of study analysis and Study 200056 Week 160 analysis), Grade 3 and 4 elevations of CK were observed in 50 subjects receiving oral CAB or CAB + RPV (m2.7.4 Section 3.1.6).

5.5.1.3. Lipase

Phase III Studies

In Studies 201584 and 201585 at Week 48, post-baseline emergent lipase elevations were observed in both treatment groups at comparable frequencies for Grade 1 (CAB + RPV 50 compared with CAR 49) and Grade 2 events (CAB + RPV 46 compared with CAR 43), although a slightly higher incidence was observed in the CAB + RPV group for Grade 3 (CAB + RPV 23 compared with CAR 10) and Grade 4 events (CAB + RPV 10 compared with CAR 6) (m2.7.4 Section 3.1.7). The majority of these changes were Grade 1 or Grade 2 and were asymptomatic.

At the Week 96 analysis in Study 201584, there were 7 additional Grade 3 or 4 post-Baseline emergent lipase elevations (2 in CAB + RPV group vs. 5 in CAR group) (m2.7.4 Section 3.1.7). At the Week 96 analysis in Study 201585, there were 5 additional Grade 3 or 4 post-Baseline emergent lipase elevations (all occurred in the Extension Switch to CAB + RPV group).

In Study 207966, there were no clinically relevant differences between treatment groups or changes from Baseline for lipase (m2.7.4 Section 3.1.7).

5.5.1.4. Bilirubin

Phase III Studies

In Study 201584 and Study 201585, isolated, asymptomatic, non-progressive total bilirubin elevations have been observed without other liver chemistry abnormalities present (including transaminases) (m2.7.4 Section 3.1.1.1). Total bilirubin elevations were mostly Grade 1 or Grade 2 (57/59 CAB + RPV; 28/31 CAR). No Grade 3 bilirubin elevations occurred. 5 Grade 4 elevations occurred (2 CAB + RPV; 3 CAR). Results from the Week 96 analysis were consistent with those reported at Week 48; few additional Grade 3 or 4 bilirubin elevations were reported between Week 48 and Week 96 in either study.

In Study 207966, small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with CAB + RPV (m2.7.4 Section 3.1.1.1). Three subjects who had elevations of both bilirubin and ALT were identified as having acute viral hepatitis.

5.5.1.5. Lipid Parameters

Phase III Studies

In Studies 201584 and 201585, a small proportion of subjects in both treatment groups had cholesterol and triglycerides changes of Grade 2 or higher at Week 48 (Table 20). The difference between CAB + RPV and CAR in the change in lipid profile from Baseline through Week 48 was not clinically significant. At the Week 96 analysis, no clinically relevant patterns in changes in NCEP fasting lipids from Baseline were observed in either study (m2.7.4 Section 3.1.8).

Table 20 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Values for Lipid Parameters during the Maintenance Phase: Week 48 Analysis (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Cholesterol (mg/dL)						
Grade 1	30 (11)	18 (6)	39 (13)	14 (5)	69 (12)	32 (5)
Grade 2	15 (5)	8 (3)	10 (3)	17 (6)	25 (4)	25 (4)
Grade 3	0	0	0	1 (<1)	0	1 (<1)
Grade 4	0	0	0	0	0	0
Triglycerides (mg/dL)						
Grade 1	14 (5)	24 (8)	20 (6)	25 (8)	34 (6)	49 (8)
Grade 2	3 (1)	5 (2)	6 (2)	6 (2)	9 (2)	11 (2)
Grade 3	2 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
Grade 4	0	0	0	0	0	0

Data Source: m2.7.4 In-text Table 79.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, minimal increases from Baseline in median total cholesterol (1.10%), LDL cholesterol (2.80%), and cholesterol/HDL ratio (1.27%) were noted for the Q4W group at Week 48 (m2.7.4 Section 3.1.8). The changes were not considered clinically significant. Results for triglycerides and HDL at Week 48 were similar in the 2 treatment groups. There were no clinically relevant patterns in changes in fasting lipids from Baseline in either treatment group.

5.5.2. Hematology

Phase III Studies

In Study 201584 and Study 201585, the changes from Baseline to Week 48 in hematology values were not clinically relevant; most hematology abnormalities were Grade 1 or 2 (m2.7.4 Section 3.2). Eleven subjects (4 CAB + RPV; 7 CAR) had Grade 3 or 4 post-Baseline emergent hematology abnormalities at Week 48. These included abnormalities in hemoglobin (n=5), neutrophils (n=4), and platelets (n=2). At the Week 96 analysis, 6 additional subjects (1 CAB + RPV; 5 CAR) had Grade 3 or 4 post-Baseline emergent hematology abnormalities (all occurred in Study 201584). These included abnormalities in hemoglobin (n=3), neutrophils (n=1), and platelets (n=2). Overall, hematology laboratory values did not significantly change over time or between treatment groups and no trends were observed.

In Study 207966, there were no clinically relevant differences between treatment groups for hematology parameters (m2.7.4 Section 3.2).

5.6. ADRs for CAB + RPV

ADRs for CAB + RPV were identified from pivotal Phase III clinical trials of CAB + RPV (Study 201584 and Study 201585 pooled analysis at Week 48) based on an analysis of pooled data at Week 48 and Phase IIIb Study 207966 at Week 48.

CAB + RPV were administered as a combination regimen (monthly and every 2 month dosing) and ADRs are listed in Table 21. ADRs listed include those attributable to both the oral and injectable formulations of CAB + RPV.

The most frequently reported ADRs from monthly dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia (10%).

The most frequently reported ADRs from ATLAS-2M every 2 month dosing were injection site reactions (76%), headache (7%) and pyrexia (7%).

The ADRs identified in these studies are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Table 21 Proposed ADRs for CAB + RPV

MedDRA System Organ Class	Frequency Category	ADRs for CAB + RPV regimen
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence Vasovagal reactions (in response to injections) [d]
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain [a] Flatulence Diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity [b]
Skin and subcutaneous tissue disorders	Common	Rash [c]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Injection site reactions (pain and discomfort, nodule, induration)[d] Pyrexia [e]
	Common	Injection site reactions (swelling, erythema, pruritus, bruising, warmth, hematoma) Fatigue Asthenia Malaise
	Uncommon	Injection site reactions (cellulitis, abscess, discoloration, anaesthesia, haemorrhage)
Investigations	Common	Weight increased

MedDRA System Organ Class	Frequency Category	ADRs for CAB + RPV regimen
	Uncommon	Transaminase increased

a. Abdominal pain includes the following grouped MedDRA preferred term: abdominal pain, upper abdominal pain.
b. Rash includes the following grouped MedDRA preferred terms: Rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
c. Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, feeling hot, body temperature increased.
d. Injection site reactions listed in the table have been reported in 2 or more subjects.

5.6.1. Local Injection Site Reactions

In each of the three Phase III studies, ≤1% of subjects discontinued treatment with CAB + RPV because of ISRs.

ISRs were the most frequent adverse events associated with the intramuscular use of CAB + RPV (Section 5.4.6.1). When dosing monthly, out of 30393 injections, 6815 ISRs were reported. When dosing every 2 months, out of 8470 injections, 2507 ISRs were reported.

The severity of reactions was generally mild (Grade 1, 70% to 75% of subjects) or moderate (Grade 2, 27% to 36% of subjects). 3 to 4% of subjects experienced severe (Grade 3) ISRs, and no subjects experienced Grade 4 ISRs. The median duration of overall ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

5.6.2. Weight Increased

At the Week 48 timepoint, subjects in Study 201584 and Study 201585 who received CAB + RPV gained a median of 1.5 kg in weight; those in the CAR group gained a median of 1.0 kg (pooled analysis) (Section 5.4.6.8). In the individual studies at Week 96, median weight gain from Baseline in Study 201584 was 2.0 kg in both treatment groups, and in Study 201585 was 2.1 kg in the CAB + RPV group and 1.1 kg in the Extension Switch to CAB + RPV group.

In Study 207966 at Week 48, median weight gains from Baseline were 1.0 kg in both treatment groups.

Similar trends with increased weight with CAB + RPV have been observed with treatment with CAB + RPV during Phase IIB studies with a median weight gain of 3.05 kg over 160 weeks (approximately 3 years) in Study 200056 and 6.50 kg at EOS (between 5 and 6 years of treatment) in Study LAI116482.

5.6.3. Changes in Laboratory Chemistries

During Phase III studies, small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with CAB + RPV (Section 5.5.1.4). These changes are not considered clinically relevant as they likely reflect competition between CAB and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Elevated transaminases (ALT/AST) were observed in subjects receiving CAB + RPV during the clinical trials. These elevations were primarily attributed to acute viral hepatitis (m2.7.4 Section 2.1.6.2). A few subjects on oral RPV + oral CAB had transaminase elevations attributed to suspected drug-related hepatotoxicity (Section 5.5.1.1).

Asymptomatic CPK elevations mainly in association with exercise, have also been observed with CAB + RPV treatment (Section 5.5.1.2).

5.7. Special Patient Populations

5.7.1. Sex, Age, and Race

The pooled analysis from Studies 201584 and 201585 at Week 48 do not suggest any effect of sex, age, or race on the safety profile of CAB (m2.7.4 Section 5.1.1).

In Study 207966, treatment differences across the Baseline characteristics; CD4+ count, age, race, BMI, and age were comparable between the two treatment groups (m2.7.4 Section 5.1.1). No clinically significant differences in the pharmacokinetics of CAB were observed based on age, sex, or race. In females with prior exposure to CAB + RPV ≥1 week, and for CAB + RPV Baseline third agent class, a statistically significant difference in proportion between treatment groups was observed.

5.7.2. Hepatitis B and/or C Virus Co-infection

HIV infected subjects with evidence of HBV coinfection were excluded from the CAB clinical program. No conclusions can be made about the safety of CAB in hepatitis B co-infected patients. The use of CAB LA was not studied in these patients. In Study 201584 and Study 201585, subjects who developed isolated ALT elevations and were identified to have acquired acute infectious hepatitis B had CAB + RPV dosing withheld. Resumption of dosing with acute HBV infection was not studied. Dosing with CAB + RPV should be discontinued and an alternative ARV regimen with HBV activity should be introduced. HIV treatment guidelines recommend NRTI-containing regimens with activity against hepatitis B virus [DHHS, 2019; EACS, 2019; IAS, 2016]. In Study 207966 at Baseline, 2 (<1%) subjects in the Q8W group and 1 (<1%) subject in the Q4W group tested positive for hepatitis B antibody [GSK Document Number 2019N406358_01]. Based upon additional testing in which all 3 subjects had HBV DNA <LLQ, these subjects were not considered to have active Hepatitis B infection and were allowed to participate in the study.

Asymptomatic subjects with stable HCV were allowed to enroll in the Phase II and Phase III trials for CAB + RPV provided that certain criteria were met. In the pooled analysis of Studies 201584 and 201585, 42 subjects on CAB + RPV and 40 subjects on CAR were determined to be co-infected with HCV at Baseline, as implied by HCV serology testing alone (m2.7.4 Section 5.1.2.2). The subjects without advanced chronic HCV were not at increased risk of developing hepatotoxicity or increased transaminases during treatment with CAB + RPV compared with subjects infected by HIV only. In Study 207966 at Baseline, 5 (<1%) subjects in the Q8W group and 6 (1%) subjects in the Q4W group tested positive for hepatitis C virus [GSK Document Number 2019N406358_01]. One subject with HCV in the Q4W group had LSC and then restarted study drug.

5.7.3. Hepatic Impairment

No dose adjustment in CAB (oral or LA) is required for patients with mild or moderate hepatic impairment (Section 3.3.1). No data are available in severe hepatic impairment.

5.7.4. Renal Impairment

No dose adjustment of oral CAB or CAB LA is required for patients with mild to severe renal impairment (creatinine clearance ≤30 mL/min and not on dialysis, Section 3.3.2). No data are available in subjects with end-stage renal disease on renal replacement therapy. CAB is highly bound to plasma proteins. Therefore, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

5.8. Pregnancy and Lactation

Throughout the CAB clinical development program, 20 subjects exposed to CAB became pregnant. Subjects who become pregnant during CAB or CAB + RPV treatment were discontinued from CAB or CAB + RPV treatment. Viral load should be closely monitored during pregnancy. Pregnancy data are discussed in m2.7.4 Section 5.4.1.

There are insufficient human data on the use of CAB during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. CAB has been detected in systemic circulation for up to 12 months or longer after single injections; therefore, consideration should be given to the potential for fetal exposure during pregnancy. The benefit-risk of using CAB with individuals during pregnancy should be evaluated by the healthcare provider on an individual basis.

CAB (oral or LA) has not been studied in mothers breastfeeding infants. Women who were breastfeeding infants were excluded from study participation.

It is not known whether CAB is secreted in human milk. It is expected that CAB will be secreted into human milk based on animal data, although this has not been confirmed in humans. CAB may be present in human milk for up to 12 months or longer after the last CAB injection.

Because of both the potential for HIV transmission and the potential for AEs in nursing infants, mothers should be instructed not to breastfeed if they are receiving CAB.

5.9. Medication Errors

Over 30,000 injections have been administered in the clinical program (Study 201584, Study 201585, Study 200056, Study 207966). Medication errors can occur based on the IM method of administration for CAB. No AEs or evidence of lack of efficacy were identified in Phase III/IIIb studies as a result of medication errors. There have been no reports of attempts to combine CAB + RPV into a single syringe. In addition, device malfunctions were reported infrequently.

In Study 201584 and Study 201585 to Week 48, medication errors occurred in 15 subjects out of the total of 14,682 injections and have included both overdosing and underdosing (m2.7.4 Section 5.6). .

In Study 207966, there were few reports of dosing errors or device malfunctions (m2.7.4 Section 5.6).

- In the Q8W group, 1 subject was underdosed (received 2 mL instead of 3 mL) with both CAB + RPV; no dosing errors were reported in the Q4W group.
- Device malfunctions were reported for 4 subjects in the Q8W group and for 3 subjects in the Q4W group.

Inadvertent partial IV injections are discussed in Section 5.4.8. Medication errors resulting in the delivery of more than the intended dose are discussed in Section 5.11.

5.10. Injection Site Selection

Due to the injection volume required for CAB LA dosing (3 mL or 2 mL), the gluteal muscle was selected early in clinical development. During clinical trials involving CAB LA, both the dorsogluteal and ventrogluteal injection sites have been used. The ventrogluteal approach is favored by current guidance for administering injections as it avoids proximity to the neurovascular bundle in the gluteal region. Therefore, this injection site will be recommended as preferred in the IFU for IM CAB treatment.

5.11. Withdrawal Effects, Abuse Potential, and Overdose

Due to the lack of psychoactive effects, there is no risk for withdrawal effects or abuse potential for CAB. Withdrawal effects with CAB have not been observed during the 1 year follow up after treatment discontinuation. No propensity for abuse potential was observed during the CAB + RPV development program.

The highest IM doses of CAB studied in the CAB + RPV development program to date are 800 mg of CAB.

Medication errors could lead to a potential overdose and are discussed in Section 5.9. No AEs have been reported in association with the medication errors in Study 201584 and

Study 201585. In Study 207966, 2 subjects had an SAE with acute symptoms believed to be secondary to high exposure to RPV (see Section 5.4.8).

Management of any occurrence of overdose should be as clinically indicated by the presenting toxicity, such as monitoring of vital signs and ECG (QT interval). CAB is known to be highly protein bound in plasma, therefore dialysis is unlikely to be helpful in removal of the drug from the body.

5.12. Post-Marketing

Oral CAB and CAB LA are not currently marketed in any country.

5.13. Safety Conclusion

The integrated analysis of safety across the Phase III clinical studies (Study 201584 and Study 201585) in combination with Phase IIIb data (Study 207966) and Phase II data (Study 200056 and Study LAI116482) supports a favorable safety profile of CAB + RPV in a monthly dosing regimen or an every 2 months dosing regimen.

Furthermore, the overall safety profile for CAB + RPV administered every 2 months was similar to the safety profile for CAB + RPV administered every month for both ISRs and non-ISR AEs.

A total of 2141 subjects have been exposed to CAB + RPV in Phase II and III/IIIb studies as of 18-OCT-2019.

There were no changes to the overall safety profile during long-term treatment; safety results at the Week 96 analyses were consistent with those at the Week 48 analyses. Few additional subjects, if any, had AESIs, and no additional SAEs assessed as drug-related were reported since the Week 48 analysis in Studies 201584 (Week 96/100) and 201585 (Week 96). Accordingly, conclusions from Studies 201584, 201585, and 207966 are based on data from the Week 48 analyses.

Common AEs

- In pooled Studies 201584 and 201585, ISRs were the most frequently reported AE but were generally well tolerated. The most common ISR was pain (77% of subjects), and ISRs were mild to moderate and self-limiting with few discontinuations (1% of subjects) due to ISRs or injection intolerance. The percentage of subjects reporting ISRs at each visit decreased over time.
- Study 207966 results were similar to the pooled results in Studies 201584 and 201585. ISRs were generally mild and of short duration; furthermore, the frequencies and types of ISRs were similar to those observed in pooled Studies 201584 and 201585. The rate of withdrawals due to injection intolerability (1% in Q8W group and 2% in Q4W group) was similar to the rate in pooled Studies 201584 and 201585.

- In pooled Studies 201584 and 201585, the most frequently (≥10% in either group) reported non-ISR AEs were nasopharyngitis and upper respiratory tract infection, both of which were reported in similar proportions of subjects in the pooled CAB + RPV Q4W and CAR groups. Non-ISR AEs more commonly reported (≥5% difference) in the pooled CAB + RPV Q4W group compared with the CAR group were headache and pyrexia.
- In Study 207966, non-ISR AEs reported by ≥10% of subjects in either the Q8W or Q4W group were nasopharyngitis and upper respiratory tract infection. Headache (Q8W: 7%; Q4W: 7%) and pyrexia (Q8W: 5%; Q4W: 8%) were reported by a similar proportion of subjects in either group.
- Drug-related AEs, as identified by the investigator, were reported with a higher incidence with CAB + RPV Q4W compared with CAR in pooled Studies 201584 and 201585. The most common (>10 subjects per group) drug-related non-ISR AEs were headache, pyrexia, nausea, fatigue, asthenia, body temperature increased, myalgia, and dizziness.
- In Study 207966, results were similar. Drug-related non-ISR AEs reported by >10 subjects in either the Q8W or Q4W group were pyrexia, asthenia, fatigue, nausea, and headache.

Grade 3 and 4 AEs

- In pooled Studies 201584 and 201585, Grade 3 and Grade 4 AEs occurred at a higher incidence with CAB + RPV compared with CAR. This difference in these reported AEs was predominantly attributable to injection site reactions, acute viral hepatitis, and also laboratory findings of elevated creatine kinase and lipase.
- There were no Grade 3 non-ISR AEs reported by ≥2 subjects that occurred in both the pooled studies and in Study 207966. Blood creatine phosphokinase increased was the only Grade 4 non-ISR AE reported in both pooled Studies 201584 and 201585 and in Study 207966 among subjects treated with CAB + RPV.

Non-fatal SAEs and Deaths

- The incidence of SAEs reported in pooled Studies 201584 and 201585 was comparable between CAB + RPV Q4W and CAR. The most frequently reported SAE with CAB + RPV Q4W occurring in more than 1 subject was hepatitis A (n=4). Only 2 SAEs were considered study drug-related by the investigator: 1 subject in the CAB + RPV Q4W treatment group had an SAE of right knee mono-arthritis and 1 subject in the CAR treatment group had an SAE of suicidal ideation. No additional SAEs or deaths were reported between the Week 48 and Week 96 analyses.
- In Study 207966, results were similar to the Phase III studies in that no trends for SAEs were apparent. Three SAEs were reported in more than 1 subject in either treatment group: pneumonia, appendicitis, and hemorrhoids. SAEs reported as possibly drug related occurred with a frequency of <1% in both groups, and each SAE PT was reported once (pancreatitis acute, injection site abscess, and presyncope in the Q8W group and hypersensitivity in the Q4W group).

- Four subjects were reported to have post-injection reactions that were SAEs; 3 with presumed inadvertant IV injection of RPV (based on PK data showing unexpectedly elevated RPV concentrations). The fourth case was not confirmed as resulting from inadvertent IV administration because a suitably timed post-dose PK sample was not collected. In Study 200056, 1 case was reported. In Study 207966, 3 cases were reported. No specific AEs have been identified as associated with unexpectedly high CAB levels. The SAEs of post-injection reactions were transient in nature and did not result in clinically significant sequelae.
- Among subjects receiving CAB + RPV during Phase III/IIIB Studies 201584, 201585, and 207966, 1 death was reported. The death (Q8W group in Study 207966) was reported 522 days after the first dose of CAB + RPV and 98 days after the subject's last dose of study drug. The cause of death was sepsis as a result of complications of acute pancreatitis (pancreatitis assessed as possibly related to study drug by the investigator). Based upon the long latency period and possible confounders, the Sponsor does not believe the evidence supports the study drugs being causative in this instance.
- There were 2 deaths during Phase III/IIIB studies in subjects in the CAR group (both accidental in nature).
- During Phase II studies, there were 6 fatalities. Of these 6 fatalities, 1 death (myocardial infarction) was considered study drug related (CAB + RPV) by the investigator. The subject had been on treatment for approximately 3 years and had several risk factors for cardiovascular disease.

AEs Leading to Withdrawal

- The rate of discontinuation was low overall for Studies 201584 and 201585. 22 (4%) subjects in the CAB + RPV group and 9 (2%) subjects in the CAR group had AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase. The most common AEs leading to withdrawal for CAB + RPV were acute viral hepatitis (n=9) and ISRs (n=5). Individual AEs leading to withdrawal had an incidence of <1%.
- In Study 207966, the rate of AEs leading to withdrawal was low (2%) with no distinct patterns of AEs between the treatment groups.

AEs of Special Interest

- There were no cases of serious reactions such as DILI or HSR in Studies 201584 and 201585 with CAB + RPV. One possible case of DILI was reported during OLI in Study 207966. No cases of DILI have occurred during CAB LA + RPV LA treatment. In Studies 201584 and 201585, there was a higher incidence of Grade 3/4 ALTs and subjects who met LSC in the CAB + RPV treatment regimen compared with the CAR regimen, which was due to the higher incidence of acute viral hepatitis occurring in subjects in the CAB + RPV group. This finding is considered to be a chance occurrence and not related to treatment with CAB+RPV
- During Phase I and Phase II, DILI was identified in 5 subjects receiving oral CAB (incidence was <1%).

- The incidence of neuropsychiatric AEs was low (up to 6% of subjects) during Studies 201584 and 201585 with CAB + RPV Q4W. The incidence of anxiety, depression, and sleep disorders with CAB + RPV Q4W was 1% to 4%. There were no serious neuropsychiatric events with CAB + RPV Q4W with 2 withdrawals (1 subject for depression suicidal and 1 subject for anxiety). In Study 207966, neuropsychiatric AESIs of depression, anxiety, and sleep disorders were reported in 2% to 7% of subjects in either treatment group, with few events leading to withdrawal.
- Weight gain was observed in Studies 201584 and 201585 with a pooled median weight gain of 1.5 kg with CAB + RPV Q4W when compared with 1.0 kg median weight gain with CAR (Week 48 analysis). This difference was more pronounced in Study 201585 with median weight gain of 1.8 kg with CAB + RPV Q4W compared with a median weight gain of 0.3 kg with CAR. It is unclear if this weight increase was due to increased adiposity as body composition was not measured in this trial. Subjects in both the Q4W and Q8W groups in Study 207966 had a median weight gain of 1.0 kg during the MP (Week 48 analysis). Similar trends with increased weight with CAB + RPV have been observed with treatment with CAB + RPV during Phase IIB studies with a median weight gain of 3.05 kg over 160 weeks (approximately 3 years) in Study 200056 and 6.50 kg at EOS (between 5 and 6 years of treatment) in Study LAI116482.
- Treatment with CAB + RPV Q4W or Q8W appears to have no clinically relevant effect on the following AESIs: QT prolongation, seizures, rhabdomyolysis, pancreatitis, or impact on creatinine.

Oral Treatment

- There were few safety events observed with oral treatment (OLI) during Studies 201584, 201585, and 207966. The overall safety profile observed with oral CAB + RPV is similar to that observed overall with the CAB + RPV treatment regimen (with the exception of ISRs). One possible case of DILI was reported during OLI in Study 207966.

Laboratory Assessments

- The majority (74.7% CAB + RPV, 80.2% CAR) of the maximum post-baseline emergent clinical chemistry abnormalities were Grade 1 or Grade 2 in intensity in pooled Studies 201584 and 201585. With the exception of creatine kinase and lipase (higher frequency in CAB + RPV), there were similar frequencies of Grade 3/4 clinical chemistry abnormalities between the treatment groups. No clinically relevant differences were observed overall in Grade 3 and Grade 4 post-Baseline emergent abnormalities between the CAB + RPV and CAR groups.
- In Study 207966, no clinically relevant patterns in changes for chemistry, hematology, or lipids from Baseline category for the Maintenance Phase through Week 48 were observed in either treatment group.

Intrinsic Factors

- Results from Studies 201584 and 201585 do not suggest any effect of age, sex, or race on the safety profile of CAB.
- In Studies 201584, 201585, 207966, and 200056, medication errors and device malfunctions were infrequent occurrences, and no AEs were directly attributable to these errors.
- Co-infection with hepatitis
  - In Studies 201584 and 201585, 42/591 subjects on CAB + RPV Q4W and 40/591 subjects on CAR were identified as co-infected with HCV at Baseline. The subjects included in the study did not have advanced chronic HCV. Of the 42 subjects in the CAB + RPV Q4W arm, none developed signs or symptoms of DILI during their study participation, although limited conclusions can be drawn about this small sub population. In Study 207966, fewer subjects (11/1044) were determined to be co-infected with HCV at Baseline, and results were similar.
  - HIV-infected patients with evidence of HBV co-infection were excluded from the CAB + RPV clinical program as CAB + RPV does not have activity against HBV. No conclusions can be made about the safety of CAB + RPV in HBV co-infected patients.
- No dose adjustment of CAB (oral or LA) is required for patients with mild or moderate hepatic impairment. No data are available in severe hepatic impairment.
- No dose adjustment of CAB (oral or LA) is required for patients with mild to severe renal impairment (creatinine clearance ≤30 mL/min and not on dialysis). No data are available in patients with end-stage renal disease on renal replacement therapy.

Special Populations

- The safety of CAB during human pregnancy and breastfeeding has not been established; CAB should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

6. BENEFITS AND RISKS CONCLUSIONS

CAB, when used with RPV, is an effective and well tolerated regimen for the maintenance of HIV-1 suppression, based on the Week 48 and Week 96 data from the 2 pivotal Phase III trials with CAB + RPV (Study 201584 and Study 201585) and the Week 48 data from the Phase IIIb trial with CAB + RPV (Study 207966). CAB + RPV is a 2-drug, NRTI-sparing injectable regimen for the long-term treatment of HIV-1 infection. The benefit/risk profile of the CAB + RPV 2-drug regimen was defined through evaluation of the efficacy, safety, and tolerability of the individual components as well as the combination through the Phase III/IIIb studies. The Phase III trials showed that CAB + RPV monthly dosing regimen is non-inferior to daily oral CAR in maintaining virologic suppression in HIV-1 infected subjects. The Phase IIIb trial (207966) showed that the CAB + RPV every 2 months dosing regimen is non-inferior to the CAB + RPV monthly dosing regimen in maintaining virologic suppression in HIV-1

infected subjects. Rates of CVF were low in CAB + RPV treatment groups. The overall safety profile was similar for both dosing regimens. The most frequently reported AE in both treatment groups was ISR, which were generally mild, self-limited, and led to a very low rate of treatment discontinuations.

6.1. Therapeutic Context

Currently, there are no approved 2-drug LA injectable regimens for treatment of HIV-1 infection. IM administration of a 2-drug combination therapy with CAB + RPV may be a convenient therapeutic option offering opportunities for improved treatment satisfaction and adherence to treatment in HIV-1 infected patients due to factors such as less frequent dosing (with options for monthly or every 2 months dosing injections) and the treatment administration being directly observed. HIV patients may also potentially avoid stigma associated with pill-taking and fewer reminders of disease status than daily oral treatments. This regimen may be an important option for some patients who are unable to take or absorb oral medications.

6.1.1. HIV-1 Infection

In 2018, an estimated 37.9 million people worldwide were living with HIV/AIDS and 1.7 million people were newly infected with HIV [UNAIDS, 2019]. In 2018, 770,000 people died from AIDS-related illness. Of the people living with HIV in 2018, 23.3 million were on ART [UNAIDS, 2019]. Increasing access to treatment is contributing to a reduction in AIDS-related deaths among adults and children, and efforts to strengthen HIV prevention and treatment programs are reducing the transmission rate of HIV. Recent trial results have confirmed that people living with an undetectable viral load do not transmit virus to uninfected contacts [Cohen, 2016].

6.1.2. Current Therapies and Unmet Medical Need

The current paradigm in the treatment of HIV involves life-long, daily, oral therapy with a combination of ARVs. Over the last 3 decades, there have been substantial improvements in the durability, safety and tolerability, and convenience of all ARV classes. Fixed-dose combinations have greatly advanced HIV treatment by allowing simplification of dosing and reduction of pill burden. However, close adherence to daily prescribed treatment is essential to achieve and maintain viral suppression and prevent emergence of viral resistance mutations [Orrell, 2017].

Although combination ART has significantly reduced AIDS-related morbidity and mortality, treatment failure and drug resistance continue to impact treated HIV-infected people. Factors contributing to these less optimal outcomes include inadequate adherence to life-long daily therapy, pre-existing or acquired drug resistance, drug-drug interactions leading to sub-therapeutic concentration of antiretroviral medication, and drug toxicities both short and long-term. Among regimens of comparable efficacy, physicians and HIV-1-infected patients who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving full adherence.

Furthermore, patients with mental illness, homelessness, drug abuse, major life events, or in adolescence face substantial adherence challenges. Even with convenient oral single tablet regimens, patients remain burdened by daily reminders of their HIV infection. Additionally, for some patients, pill packs within the patient's home and personal environment may be associated with stigma. More discreet treatment options may avoid stigma associated with daily oral therapy. Consequently, there continues to be a medical need for the development of novel antiretroviral agents and new approaches to improve therapy compliance.

An injectable, long-acting, 2-drug regimen for the treatment of HIV-1 addresses some of the treatment issues currently facing patients infected with HIV. The option for monthly dosing or every 2 months dosing with the CAB + RPV injectable regimen provides a durable therapy that is expected to improve adherence and treatment satisfaction.

6.2. Benefits of CAB + RPV in the Treatment of HIV-1 Infection

New therapeutic options that combine potency, tolerability, and ease of use are needed for all sectors of the HIV population. There is substantial evidence in the literature that supports the benefit of streamlined treatment regimens. Further, data indicate that patients prefer less frequent dosing; adherence benefits are important given that HIV is a lifelong, currently incurable infection.

CAB, when used with RPV in a 2-drug, NRTI-sparing regimen, is intended for the long-term treatment of HIV-1 infection. CAB is a potent INSTI with proven efficacy and a well-established safety profile. Based on Week 48 data from the 2 large pivotal Phase III clinical studies (Study 201584 and Study 201585) and the Phase IIIb Study 207966, CAB + RPV is an effective maintenance regimen for the treatment of HIV-1 infection. Once-monthly CAB + RPV is non-inferior to daily oral SOC (CAR) therapy in maintaining virologic suppression in HIV-1 infected subjects. The few discontinuations prior to Week 48 show that the regimen is well tolerated. The CAB + RPV every 2 months dosing regimen was demonstrated to be non-inferior to the CAB + RPV monthly dosing regimen in Study 207966 (Week 48). Few cases of confirmed virologic failure were observed and few discontinuations occurred across the Phase III/IIIb studies.

CAB, when used in combination with RPV as a 2-drug injectable treatment regimen, has distinct benefits for virally suppressed HIV-1 infected patients:

- Subjects on the every 2 months dosing regimen maintained HIV-1 suppression comparable to those on the monthly dosing regimen. Subjects on the monthly dosing regimen maintained HIV-1 suppression comparable to those on their standard of care regimen.
- CAB + RPV targets HIV replication at both the early and the late stage of the virus life cycle resulting in durable maintenance of viral suppression with a low risk of virologic failure.
- CAB + RPV can be administered on an infrequent basis (eg. monthly or every 2 months), may improve adherence to therapy and extend opportunities for therapeutic intervention to underserved patient populations. Infrequent dosing provides relief for

patients from the daily reminders of their HIV infection imposed by daily oral ART. Discreet dosing may also help recipients to avoid stigma.

- After the OLI, monthly injections eliminate the need for daily oral dosing. Therefore, the CAB + RPV regimen offers far fewer reminders of disease status; maintenance therapy may entail 6 or 12 dosing visits per year compared with daily dosing with oral SOC.
- CAB has limited DDI liabilities, enabling co-dosing with many commonly used medications. Only strong UGT inducers are contraindicated for dosing concurrently with CAB.
- Compliance with the scheduled visit windows was high in all Phase III/IIIb studies. Dosing flexibility is inherent to the dosing schedule, with allowable windows of ±7 days from the target injection date. Under exceptional circumstances, oral once-daily treatment with CAB + RPV can be used as oral therapy for short periods of time to cover planned pauses in IM dosing (eg, travel). Oral therapy can be used in place of 1 every-2-months injection visit or 2 monthly injection visits, and the overall time since the last dose will determine how LA dosing should be resumed, which should be done as soon as possible and as recommended.
- Since the CAB + RPV regimen is administered as a directly observed therapy, there is a high probability that patients will be fully compliant with the regimen.
- CAB + RPV is as effective in subjects who have recently achieved a suppressed viral load (median 16 weeks suppressed in Study 201584) as it is in subjects whose viral suppression is much longer (median 4.3 years on therapy in Study 201585). Rates of HIV-1 RNA ≥50 c/mL per the Snapshot algorithm were similar between Study 201584 and Study 201585, suggesting that the duration of SOC ART treatment prior to the initiation of monthly IM CAB + RPV does not impact virologic non-response rates overall.
- Low risk of CVF (n=7) with the use of this novel LA 2-drug regimen was identified in Study 201584 and Study 201585. Low rates of phenotypic drug resistance were observed: RPV (5/591, 0.8%), CAB (4/591, 0.7%), and 2-drug resistance (3/591, 0.5%) among CVFs. In Study 207966, protocol defined CVF occurred in <1% of subjects (8 subjects [1.5%] in the Q8W treatment group and 2 subjects [0.4%] in the Q4W treatment group) through Week 48 (including subjects with dosing beyond Week 48). In vitro phenotypic RPV resistance was present in 9 subjects and 4 subjects had CAB resistance. Based on results from these studies, multi-class treatment options, including the INI DTG, exist for subjects who fail with ART resistance.
- Overall, the Phase III/IIIb studies included a high percentage of female subjects (approximately 27% of subjects across studies). Results in women and men were consistent, suggesting that the CAB + RPV regimen is suitable for both females and males.
- Results from the Phase III/IIIb studies suggest that CAB + RPV is an effective and well tolerated regimen in individuals >50 years of age (i.e. no evidence of poorer tolerability or reduced efficacy in older compared with younger adults). CAB + RPV is an NRTI-sparing regimen that has a number of features that could be

considered to favor use in older individuals with medical co-morbidities or who may be receiving multiple other medications, which include reduced oral pill burden and food requirements, limited DDI, favorable safety profile, and enhanced ART dosing compliance.

- Given the high treatment satisfaction with and preference for the CAB + RPV regimen in the Phase III/IIIb studies, continued treatment adherence and durable viral suppression can be anticipated beyond the trial context. Subjects on the every 2 months dosing regimen expressed a high rate of preference for the every 2 months dosing regimen compared with those on the monthly dosing regimen.

6.3. Risks Associated with CAB + RPV in the Treatment of HIV-1 Infection

Clinical trials have shown that there are no clinically significant interactions between CAB and RPV. There are no shared metabolic pathways between CAB and RPV, and no common target organs were identified in respective non-clinical studies. As such, there are no pharmacologic data that would predict increased safety risk for the combination of CAB + RPV beyond those effects associated with the individual components.

Overall, 2141 subjects were exposed to oral and/or LA CAB + RPV during ViiV Healthcare sponsored HIV treatment clinical trials in Phase II and Phase III/IIIb (LA116482, 200056, 201584, 201585, 207966) as of 18 October 2019.

The main risks for consideration when prescribing CAB, when used in combination with RPV, are:

- Drug-induced hepatotoxicity (DILI) has been observed in subjects on oral therapy with CAB; it was mild or moderate and was reversible upon discontinuation of treatment. No cases of DILI were associated with use of CAB LA + RPV LA. DILI is an ADR for CAB.
- HSR has been associated with other members of the INSTI class. No cases of HSR of the type labelled for other INSTIs have been observed with CAB.
- Local ISRs were very common with the first dose of IM CAB and decreased in frequency with continued dosing. The majority of ISRs consisted of mild to moderate pain/discomfort localized to the injection site and were short lived. Significant episodes of pain were uncommon and did not typically recur in subsequent injections. Discontinuations due to ISRs were uncommon. The use of acetaminophen or NSAIDs may be beneficial in ameliorating symptoms occurring post injection. ISRs are an ADR for CAB.
- Plasma concentrations of CAB may persist for longer than 1 year in some patients after administration of the last IM dose. Following discontinuation of CAB for any reason, patients should be initiated on active SOC to minimize the risk of emergent viral resistance to CAB.
- Four cases of post-injection reactions were observed with RPV injections in Study 207966 and Study 200056. These types of events were not observed in any of the other clinical studies and the Sponsor expects these to be very rare occurrences.

- Neuropsychiatric events (anxiety, depression, sleep disorders, mood disorders, and suicidal ideation and behavior) have been observed with treatment with CAB + RPV. The highest incidence of events observed were in the categories of depression, anxiety, and sleep disorders, and these are listed as ADRs for CAB.
- Weight gain has been associated with treatment with CAB + RPV during the clinical development program. Weight gain was observed in Study 201584 and Study 201585 with a pooled median weight gain of 1.5 kg with CAB + RPV compared with 1.0 kg median weight gain with CAR. A median weight gain of 1.0 kg was observed in both treatment groups in Study 207966. Similar trends of weight increase with CAB + RPV treatment have been observed during Phase II trials. Weight increase is an ADR for CAB.

6.4. Benefit-Risk Assessment

The efficacy and safety data presented in this application for CAB, when used with RPV as a 2-drug monthly or every 2 months dosing regimen, support a favorable risk-benefit profile in the indicated HIV-1 infected population.

CAB + RPV was non-inferior to guideline recommended SOC (CAR) in maintaining HIV-1 suppression through Week 48 in the pooled analysis and in each of the pivotal Phase III Studies (Study 201584 and Study 201585). Study 207966 demonstrated that every 2 months dosing is noninferior to monthly dosing.

CAB + RPV was not found to increase risk of plasma HIV-1 RNA ≥50 c/mL in Study 201584 and Study 201585 compared with CAR. Every 2 months dosing was comparable to monthly dosing with respect to the primary efficacy endpoint of plasma HIV-1 RNA ≥50 c/mL in Study 207966. The number of subjects on CAB + RPV with CVF and resistance was low in all Phase III/IIIb studies.

The CAB + RPV monthly or every 2 months dosing regimen provides an acceptable safety profile and efficacious treatment option for patients living with HIV-1. The majority of ADRs reported in Phase III/IIIb studies have not been treatment limiting and injection tolerability has been favorable overall, with few discontinuations.

The CAB + RPV monthly or every 2 months dosing regimen is expected to provide greater treatment satisfaction and improved adherence to treatment in virologically suppressed patients due to less frequent dosing. Improved overall satisfaction with the regimen may result in increased patient compliance, especially in patients who have challenges with daily oral dosing, and as a more convenient alternative to oral therapy. Overall, the anticipated risks are considered manageable and therefore supportive of a positive benefit/risk balance. The data presented in this application support a favorable risk-benefit profile for the 2-drug CAB + RPV monthly or every 2 months dosing regimen in the indicated HIV-1 infected population.

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APPENDIX – EXPLANATIONS FOR EMPTY MODULES

The following provides a brief justification for the absence of modules in Module 5.

Module	Title	Explanation
5.1	Table of Contents	Electronic CTD Submitted
5.3.1.2	Comparative BA and bioequivalence (BE) Study reports and related information	No comparative BA or BE studies were conducted for CAB.
5.3.1.3	In Vitro - in Vivo correlation Study reports and related information	No IVIVC studies were conducted for CAB. The in vitro dissolution data are presented in m2.7.1.
5.3.2.1	Plasma protein binding Study reports and related information	Plasma protein binding data are included in m5.3.5.1 and m5.3.4.2.
5.3.2.3	Reports of studies using other human biomaterials	Reports of studies using other human biomaterials are in m4.2.
5.3.3.3	Intrinsic factor PK Study reports and related information	Hepatic and renal impairment studies are included in 5.3.3.1. PGx from Study 200056 are included in 5.3.4.2.
5.3.5.2	Study reports and related information of uncontrolled clinical studies	All studies conducted with CAB were controlled studies, hence there are no reports of uncontrolled studies.
5.3.6	Reports of postmarketing experience	CAB is not currently marketed.
5.3.7	Case Report Forms and Individual Patient Listings	Available upon request.